BURNS

PATHOLOGY AND THERAPEUTIC APPLICATIONS

AFRICA	BUTTERWORTH & CO (AFRICA) LTD DURBAN 33/35 BEACH GROVE
AUSTRALIA	BUTTERWORTH & CO (AUSTRALIA) LTD SYDNEY 8 O'CONNELL STREET MELBOURNE 430 BOURKE STREET BRISBANE 240 QUEEN STREET
CANADA	BUTTERWORTH & CO (CANADA) LTD TORONTO 1367 DANFORTH AVENUE
NEW ZEALAND	BUTTERWORTH & CO (AUSTRALIA) LTD WELLINGTON 49/51 BALLANCE STREET AUCKLAND 35 HIGH STREET

BURNS

PATHOLOGY AND THERAPEUTIC APPLICATIONS

SIMON SEVITT

MD MSc MA FRCPI DPH

Consultant Pathologist to the Birmingham Accident Hospital and M R C Burns Research Unit
External Examiner in Pathology to the Irish Conjoint Board Formerly Specialist Pathologist and Major Royal Army Medical Corps and Research Fellow to the Medical Research Council of Ireland at the School of Pathology Trinity College Dublin

LONDON

BUTTERWORTH & CO (PUBLISHERS) LTD

1957

To

Betty, Michael, Peter and Brian

PREFACE

THE clinical and pathological studies on burns have been closely connected and the mainspring of some of the best investigations on burns pathology has been the improvement of therapy. A book devoted to the pathology and disordered physiology after burning should therefore incorporate the practical applications and therapeutic lessons. No apology is needed for this since the challenge of clinical problems has stimulated many clinico-pathological and experimental investigations which have shown that certain pathological effects can be modified by therapy. These studies have been supplemented by experiments of a more theoretical and academic nature, some of which have later had a practical application. Of course the pathology of burns is not divorced from general pathology, the principles of which are applicable to the disorders which follow burning. For example, the inflammatory reaction and the healing process of the skin are special illustrations of the phenomena of inflammation and repair, and the haemodynamic effects, biochemical and metabolic disorders, electrolyte and water imbalance, renal dysfunction, endocrine changes and other sequelae and complications have parallels in other branches of medicine and surgery. Nevertheless, the pattern of changes in burned patients is unique. Their study has contributed to the understanding of normal body processes and has helped to develop general pathology.

Knowledge of the pathology of burns is widely diffused in the international medical literature, and the present work is an attempt to bring this together within the covers of a book of reasonable size. Considerable knowledge has been gained during the last twenty years and the newer and older facts are presented in this book. The advances in knowledge reflect the general progress of medicine and partly result from technical advances which include methods for measuring plasma and red cell volume, the development of histochemistry, flame photometry and steroid chemistry, the use of radioactive tracers, electrophoresis, chromatography and cardiac catheterization, as well as established histological, biochemical, haematological, bacteriological and other procedures.

This is the first book in English devoted to the pathology of burns, although there are a number of excellent monographs on treatment. It is my hope that it adequately fills the gap in medical literature. A wide range of topics is discussed, and whilst the approach is

CONTENTS

basically functional, morphology has not been neglected and has been stressed when it is the basis of understanding The influence of treatment on function and structure is dealt with and I have attempted to interpret the significance of pathological findings and to correlate functional and other changes with clinical effects The recent advances in knowledge have solved a number of problems, but new problems, at a higher level of understanding, have emerged and these have been posed in the various chapters I have tried to maintain a critical attitude throughout the book, to accept only the results of experiments and investigations which have been adequately performed and to discard ideas and theories which new facts have undermined or which are not supported by facts When important differences of opinion have arisen I have presented the different ideas and their factual basis with the intention, if I may borrow a Chinese proverb, of "letting all schools of thought contend", but I have not shirked from giving my own opinions The results of nearly ten years' experience of burns pathology, including a number of hitherto unpublished studies, have been included in the text

The book has been planned in two main parts Chapters 1 to 5 are concerned with the skin, and much of Chapter 8 on mortality and causes of death is an introduction to Chapters 9 to 22 which deal with the various body systems and organs Chapters 6 and 7 are concerned with infection and its control, whilst Chapters 23 and 24 deal with special kinds of burns In the reader's interest the clinical and therapeutic lessons are dealt with, as far as possible, under special headings at the ends of chapters This has not always been possible, and many implications are discussed in the general text With a few exceptions the illustrations are original Some have been published before in various medical journals, but most of them have been specially made for this book from material collected and prepared at the Birmingham Accident Hospital

It is my hope that the book will be of interest to surgeons, pathologists and other doctors concerned with burned patients either regularly or occasionally, that it will be of use to postgraduate students of surgery and pathology, and that the references will help the more specialized reader

SIMON SEVITT

June 1957

ACKNOWLEDGEMENTS

EVEN a work by a single author is to some extent a collective effort and this book is not an exception My thanks are due to various colleagues and friends for their interest and help at different stages of its birth Professor M H O Connor Professor of Pathology at the Royal College of Surgeons Dublin and Dr I G Graber read the whole text Mr Douglas Jackson read a considerable part and various chapters were read by Drs E J L Lowbury and Elizabeth Topley I am grateful to them for helpful suggestions and criticisms —but they are not responsible for the opinions expressed in the book I would also like to take the opportunity of expressing my thanks to the Medical Research Council for the facilities provided in the Burns Research Unit in Birmingham for the study of burns pathology during the last 10 years Miss J M Levi and Dr C N D Cruickshank kindly carried out special investigations at my request the results of which they have allowed me to publish and other colleagues have also generously permitted me to use unpublished observations Individual acknowledgements have been made in the various chapters and lists of references For special information on electrical injuries I am indebted to Mr S J Emerson Senior Electrical Inspector of the Ministry of Labour who also gave permission to use a private report My thanks are due to Dr L Crome who translated to me a large number of articles in Russian Various libraries were generous in the facilities provided especially the library of the Birmingham Medical School and I am most appreciative of the help given by Miss M P Russell and her staff I am also indebted to various colleagues for permission to re publish a number of illustrations and Table I and to the editors and publishers of the various journals in which they originally appeared Individual acknowledgements have been made in the legends A number of my own illustrations are also re published and I acknowledge the permission granted by the editors and publishers of the *Proceedings of the Royal Society of Medicine* (for Figs 2 and 23) the *Journal of Pathology and Bacteriology* (for Figs 18 and 64) the *Journal of Clinical Pathology* (for Figs 49 51 52 and 54) and the *British Medical Journal* (for Figs 58 59 and 69)

The illustrations were prepared by the Photographic Department of the Birmingham Accident Hospital most of them by Mr R. Gill and some by Mr C Richardson My thanks are due to both for their skill and technical assistance

ACKNOWLEDGEMENTS

EVEN a work by a single author is to some extent a collective effort and this book is not an exception My thanks are due to various colleagues and friends for their interest and help at different stages of its birth Professor M H O Connor Professor of Pathology at the Royal College of Surgeons Dublin and Dr I G Graber read the whole text Mr Douglas Jackson read a considerable part and various chapters were read by Drs E J L Lowbury and Elizabeth Topley I am grateful to them for helpful suggestions and criticisms —but they are not responsible for the opinions expressed in the book I would also like to take the opportunity of expressing my thanks to the Medical Research Council for the facilities provided in the Burns Research Unit in Birmingham for the study of burns pathology during the last 10 years Miss J M Levi and Dr C N D Cruickshank kindly carried out special investigations at my request the results of which they have allowed me to publish and other colleagues have also generously permitted me to use unpublished observations Individual acknowledgements have been made in the various chapters and lists of references For special information on electrical injuries I am indebted to Mr S J Emerson Senior Electrical Inspector of the Ministry of Labour who also gave permission to use a private report My thanks are due to Dr L Crome who translated to me a large number of articles in Russian Various libraries were generous in the facilities provided especially the library of the Birmingham Medical School and I am most appreciative of the help given by Miss M P Russell and her staff I am also indebted to various colleagues for permission to re publish a number of illustrations and Table I and to the editors and publishers of the various journals in which they originally appeared Individual acknowledgements have been made in the legends A number of my own illustrations are also re published and I acknowledge the permission granted by the editors and publishers of the *Proceedings of the Royal Society of Medicine* (for Figs 2 and 23) the *Journal of Pathology and Bacteriology* (for Figs 18 and 64) the *Journal of Clinical Pathology* (for Figs 49 51 52 and 54) and the *British Medical Journal* (for Figs 58 59 and 69)

The illustrations were prepared by the Photographic Department of the Birmingham Accident Hospital most of them by Mr R. Gill and some by Mr C Richardson. My thanks are due to both for their skill and technical assistance

ACKNOWLEDGEMENTS

EVEN a work by a single author is to some extent a collective effort and this book is not an exception My thanks are due to various colleagues and friends for their interest and help at different stages of its birth Professor M H O Connor Professor of Pathology at the Royal College of Surgeons Dublin and Dr I G Graber read the whole text, Mr Douglas Jackson read a considerable part and various chapters were read by Drs E. J L Lowbury and Elizabeth Topley I am grateful to them for helpful suggestions and criticisms —but they are not responsible for the opinions expressed in the book. I would also like to take the opportunity of expressing my thanks to the Medical Research Council for the facilities provided in the Burns Research Unit in Birmingham for the study of burns pathology during the last 10 years Miss J M Levi and Dr C N D Cruickshank kindly carried out special investigations at my request the results of which they have allowed me to publish, and other colleagues have also generously permitted me to use unpublished observations Individual acknowledgements have been made in the various chapters and lists of references For special information on electrical injuries I am indebted to Mr S J Emerson Senior Electrical Inspector of the Ministry of Labour who also gave permission to use a private report. My thanks are due to Dr L Crome who translated to me a large number of articles in Russian Various libraries were generous in the facilities provided, especially the library of the Birmingham Medical School and I am most appreciative of the help given by Miss M P Russell and her staff I am also indebted to various colleagues for permission to re-publish a number of illustrations and Table I and to the editors and publishers of the various journals in which they originally appeared Individual acknowledgements have been made in the legends A number of my own illustrations are also re published and I acknowledge the permission granted by the editors and publishers of the *Proceedings of the Royal Society of Medicine* (for Figs 2 and 23) the *Journal of Pathology and Bacteriology* (for Figs 18 and 64) the *Journal of Clinical Pathology* (for Figs 49 51 52 and 54) and the *British Medical Journal* (for Figs 58 59 and 69)

The illustrations were prepared by the Photographic Department of the Birmingham Accident Hospital most of them by Mr R Gill and some by Mr C Richardson My thanks are due to both for their skill and technical assistance

CHAPTER 1

TRANSFER OF HEAT TO AND THROUGH THE SKIN

AN UNDERSTANDING of the changes which occur in the skin from burns and scalds must take into account the mode duration and temperature of burning Upon these depend the temperatures and tissue changes at the skin surface and deeper levels

TRANSFER TO THE SKIN

Heat may be brought to the skin by convection radiation or conduction Transfer by conduction has much greater power to heat the skin and produce burning than heat transfer by other means

Convection—Heat is transported by a current of hot gas The rate of transfer to the skin depends on the temperature of the gas its velocity its nature and on the temperature of the skin surface

Hot air flowing at normal eddy current rate (about 1 6 kilometres per hour) transports only about 0 4 calorie per square centimetre per minute to the skin when its temperature is 100 C and the skin temperature 40 C whilst air at 400 C transports 4 calories per square centimetre per minute (Henriques and Moritz, 1947) As this heat is absorbed by the skin its surface temperature will rise and the uptake of heat will fall

Steam at 100°C transports under the same conditions as much as 300 calories per square centimetre per minute because of its high latent heat of condensation For this reason steam produces much severer burns than hot air

Blasts of hot air varying from 100° to 500°C were used by Ashe and Roberts (1945) who studied the minimum time of exposure required to produce persistent redness and blister burning in human volunteers. Persistent erythema was caused by air at 100° 200° 300° 400° and 500°C in 4–5 seconds 1 5 seconds, 0 6 0 2 and 0 1 second respectively Air blasts at the same temperatures caused blistering in 7–10 and 2–3 seconds and 0 7 0 25 and 0 2 second respectively The time-temperature curves were exponential but for blister burning there was greater deviation from a simple exponential function

Radiation.—Heat energy mainly in the infra red part of the spectrum, is radiated from a hot source in linear fashion and when it meets the skin part is absorbed and part is reflected from the surface The

Mrs M Swinden, my secretary, has been responsible for the arduous task of typing and retyping accurate copies of the manuscript and it is a special pleasure to thank her for performing the considerable addition to her work skilfully, speedily and cheerfully, and also for many other items of assistance

For help in the painstaking and time-consuming task of proofreading my thanks go to Dr and Mrs I G Graber and my son Michael

I am grateful to Messrs Butterworths for their co-operation, and in particular to Mr J K Burgess

Finally, I wish to thank my wife for her encouragement, support and sound advice

S S

This simplified picture is modified by various factors including site variations in the thickness of the epidermis and dermis various physiological factors such as the cooling effect of the blood flow (which may alter during burning) and on any oedema which may form during the burning episode A theoretical and experimental study of this complex matter was made by Moritz and Henriques (Henriques and Moritz, 1947 Moritz and Henriques 1947 Henriques, 1947 Moritz, 1947) They measured the heat capacities and conductivities of pig epidermis dermis subcutaneous fat and muscle The heat capacities are high because of the high water content of tissues—0 86 0 77 0 55 and 0 9 calorie per gramme respectively—but the conductivities are low hence the insulating effect of skin As a result of experimental and theoretical considerations they developed a general theory of heat flow through the skin This enabled them to estimate the time temperature relationship during burning within the epidermis and at the epidermo-dermal junction They demonstrated the important difference between the mode of transfer of heat by conduction on the one hand and by convection or radiation on the other For a given source temperature burning by conduction has at least a thousand times greater power to injure the epidermis than burning by radiation or by convection of relatively immobile air This is because contact and conduction raises the surface temperature of the skin immediately to that of the source whilst radiation and convection raise the surface temperature relatively slowly

Temperature gradient.—This is the difference or gradient of temperature between the surface and the deeper layers of the skin Experimental work on this gradient has been carried out by Mendelssohn and Rossiter (1944) Henriques and Moritz (1947) and by the author using contact burns. A hypodermic needle with a copper-constantan thermocouple in its tip was inserted into the subdermis, a constant temperature burning iron was applied to the skin surface superficial to the needle point, and the temperature of the subdermis was recorded every few seconds The application of the burning iron is immediately followed by a rapid increase in the subdermal temperature the unsteady state followed by a period of temperature equilibrium the steady state Fig 1 shows a typical result The subdermal temperature was 36 C and the temperature of the burning iron was 60 C Application of the burner was followed by a rapid rise in the subdermal temperature (44 at 5 seconds) then a slower rise (46 and 48 at 10 and 20 seconds respectively) until the subdermal temperature finally stabilized at about 50 C During the unsteady

rate of uptake of energy by the skin depends on the absolute temperature of the source, its radiation spectrum and effective emissivity of heat, the square of the distance between the source and the skin, the absorptivity and conductivity of skin and on certain constants The skin is also losing heat by radiation so that the effective rate of uptake is the difference between the rate of heat gain and heat loss

The main factors which influence burning are source temperature, distance and time of exposure Prolonged exposure to the sun's rays does not produce burning from heat (sunburn is due to ultra-violet radiation), but given a radiant source the temperature of which is thousands of degrees Centigrade, burning can occur within a fraction of a second if the distance from the source is relatively small

Conduction—Heat is conducted from a hot solid or liquid in direct contact with the skin Burns from hot liquids or *scalds* are essentially the same as those due to hot solids The temperature of the skin surface rises instantaneously to that of the heat source and is maintained at this temperature during the period of contact when the heat source does not cool during the burning episode, that is when its heat capacity is high or when the period of contact is limited This explains why burning by immersion in hot water causes more severe burns than for example the spilling of water at the same temperature for the same period on the skin In the former event the heat source may be considered as having an infinite heat capacity and does not cool during the burning unlike the water which causes the scald by spilling Similarly burns from the spilling of hot fluids which rapidly evaporate, such as hot alcohol, are less severe than burns from water at the same temperature Burns by molten metals are deep because of the high temperature of the metal and its latent heat of solidification

TRANSFER OF HEAT THROUGH THE SKIN

Normally the temperature of the surface of the skin is lower than the temperature of the dermis, but if heat is to be transferred from the heat source through the skin, the temperature of the skin surface must rise above that of the dermis This can be achieved through heat conduction, convection or radiation from the source Once the temperature of the skin surface is sufficiently raised heat will flow towards the dermis and raise the temperature of the skin at different levels The rate of transfer of heat depends on the heat capacity of the skin and on its thermal conductivity, that is on its powers to take up and transport heat The initial effect is a rapid uptake of heat but after a time the skin becomes heat-saturated, the heat flow then depends on thermal conductivity and skin surface temperature

This simplified picture is modified by various factors including site variations in the thickness of the epidermis and dermis various physiological factors such as the cooling effect of the blood flow (which may alter during burning) and on any oedema which may form during the burning episode A theoretical and experimental study of this complex matter was made by Moritz and Henriques (Henriques and Moritz, 1947 Moritz and Henriques 1947 Henriques, 1947 Moritz, 1947) They measured the heat capacities and conductivities of pig epidermis dermis subcutaneous fat and muscle The heat capacities are high because of the high water content of tissues—0 86 0 77 0 55 and 0 9 calorie per gramme respectively—but the conductivities are low hence the insulating effect of skin As a result of experimental and theoretical considerations they developed a general theory of heat flow through the skin This enabled them to estimate the time–temperature relationship during burning within the epidermis and at the epidermo-dermal junction They demonstrated the important difference between the mode of transfer of heat by conduction on the one hand and by convection or radiation on the other For a given source temperature burning by conduction has at least a thousand times greater power to injure the epidermis than burning by radiation or by convection of relatively immobile air This is because contact and conduction raises the surface temperature of the skin immediately to that of the source whilst radiation and convection raise the surface temperature relatively slowly

Temperature gradient.—This is the difference or gradient of temperature between the surface and the deeper layers of the skin Experimental work on this gradient has been carried out by Mendelssohn and Rossiter (1944) Henriques and Moritz (1947) and by the author using contact burns A hypodermic needle with a copper–constantan thermocouple in its tip was inserted into the subdermis, a constant temperature burning iron was applied to the skin surface superficial to the needle point, and the temperature of the subdermis was recorded every few seconds The application of the burning iron is immediately followed by a rapid increase in the subdermal temperature the unsteady state followed by a period of temperature equilibrium, the steady state Fig 1 shows a typical result The subdermal temperature was 36 C and the temperature of the burning iron was 60 C Application of the burner was followed by a rapid rise in the subdermal temperature (44 at 5 seconds) then a slower rise (46 and 48 at 10 and 20 seconds respectively) until the subdermal temperature finally stabilized at about 50 C During the unsteady

state the temperature gradient between the surface and the subdermis rapidly diminished as heat was being absorbed and transferred to deeper levels The temperatures of all the skin layers must have risen and the temperature difference between any particular layer and the surface must have fallen in a fashion similar to that observed between the subdermis and the surface The final steady state indicates equilibrium between heat gain and heat loss in the subdermis and heat "saturation" of the skin

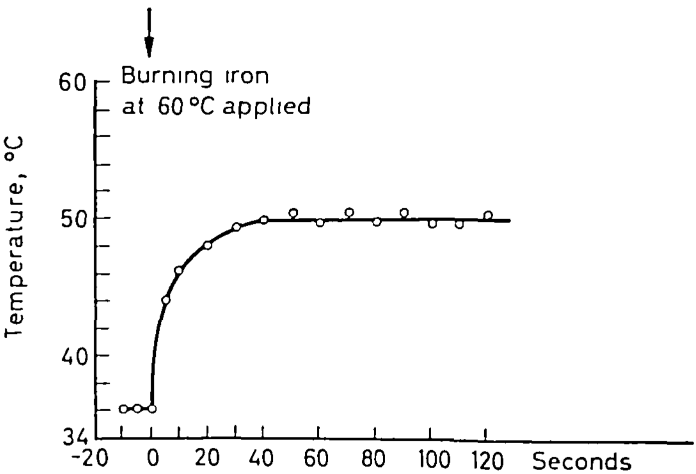


FIG 1 —Serial temperatures in the subdermis during the application of a burning iron at 60 C on the shaved abdomen of a guinea-pig A rapid rise of temperature (unsteady state) is followed by a slower rise, and finally a constant temperature of about 50 C is reached (steady state) The unsteady state signifies a rapid uptake of heat to satisfy the thermal capacity of the skin, whilst the steady state indicates equilibrium between heat gain from the burning iron and heat loss from thermal conductivity to the deeper tissues

Effects of burning at different layers in the skin The quality and duration of the vertical gradient of temperature during burning determines the subsequent changes at different levels in the skin Different combinations of temperature and duration of burning can produce similar pathological changes in the epidermis, such as necrosis or similar pathological changes in the subepidermal capillary plexus whilst the deeper changes at different levels in the dermis may be quite different depending on the temperatures reached For example Fig 2 shows in contact burns of the guinea-pig the minimal combinations of temperature and duration of burning which just produce a permeability increase in the dermal vessels (curve PP) This was established by the slight but definite appearance of blue

dye in the burned skin after the introduction of Evans blue into the blood stream (Sevitt 1954) The minimal permeability response occurred after burning at 58 C for 5 seconds 54 for 30 seconds 52 for 60 seconds, 50 for 3 minutes and so on However the prolonged burns must have heated the dermis to a greater depth than the shorter ones and the changes below the superficial capillary plexus will have differed

Different vertical gradients of temperature produce different vertical gradients of damage in all the constituents of the dermis

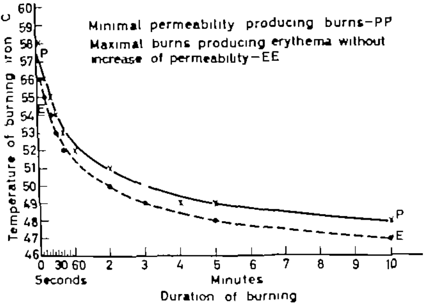


FIG 2.—The minimal temperatures and periods of application of the burning iron which just produce an increase of permeability in the dermal capillaries of the guinea pig. Combinations at and above curve PP produce an increase of permeability but at and below EE erythema is the only visible evidence of burning.

The most severely damaged tissues are the superficial ones, and in the dermis there is a gradient of damage to the hair follicles and sweat ducts and to the capillary network Thus the depths of dermal epithelial necrosis increased capillary permeability and capillary stasis are determined by the duration and nature of the vertical gradient of temperature during burning In other words the depth and nature of the inflammatory reaction in the skin including probably the protein concentration of the exudate as well as the manner of healing and the clinical course of the burn are determined by this vertical gradient This does not mean that they are not influenced by subsequent events including therapy

state the temperature gradient between the surface and the subdermis rapidly diminished as heat was being absorbed and transferred to deeper levels The temperatures of all the skin layers must have risen and the temperature difference between any particular layer and the surface must have fallen in a fashion similar to that observed between the subdermis and the surface The final steady state indicates equilibrium between heat gain and heat loss in the subdermis and heat "saturation" of the skin

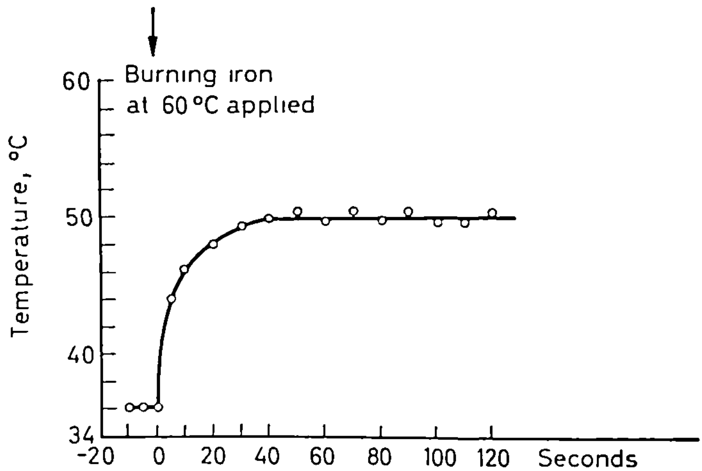


FIG 1 —Serial temperatures in the subdermis during the application of a burning iron at 60° C on the shaved abdomen of a guinea-pig A rapid rise of temperature (unsteady state) is followed by a slower rise, and finally a constant temperature of about 50°C is reached (steady state) The unsteady state signifies a rapid uptake of heat to satisfy the thermal capacity of the skin, whilst the steady state indicates equilibrium between heat gain from the burning iron and heat loss from thermal conductivity to the deeper tissues

Effects of burning at different layers in the skin —The quality and duration of the vertical gradient of temperature during burning determines the subsequent changes at different levels in the skin Different combinations of temperature and duration of burning can produce similar pathological changes in the epidermis, such as necrosis, or similar pathological changes in the subepidermal capillary plexus, whilst the deeper changes at different levels in the dermis may be quite different depending on the temperatures reached For example, Fig 2 shows in contact burns of the guinea-pig the minimal combinations of temperature and duration of burning which just produce a permeability increase in the dermal vessels (curve PP) This was established by the slight but definite appearance of blue

CHAPTER 2

CELLULAR HYPERTHERMIA AND THE HISTOLOGY OF BURNED SKIN

THE EFFECTS of heat on skin are important because they may lead to profound systemic changes such as oligaemic shock anaemia renal failure and metabolic disorders and also because of the light they have shed on such general biological problems as necrosis inflammation healing and infection

The reactions of skin to heat may be divided into (1) direct tissue damage and (2) an inflammatory reaction (Chapter 3) These effects are related first because they are manifestations of heat injury to physiologically different cells and secondly because they are dynamic changes altering with time and influencing one another

For purposes of discussion the tissue changes will be considered under two main headings cellular hyperthermia and the histological changes in burned skin

CELLULAR AND BODY HYPERTHERMIA

All animals plants bacteria and viruses are sensitive to heat but there is considerable variation in the temperatures which they can withstand Plants generally die at between 40 and 50 C and animals at between 30 and 45 C but different genera and species in both kingdoms vary greatly Many bacteria are killed below 60°C within half an hour others can survive 70°C and bacterial spores usually require temperatures between 100° and 120°C before they die Some algae normally live at 53 C infusoria have been found in springs at over 80°C and even tadpoles have been observed in the hot springs of Yellowstone Park (quoted by Cameron 1952) Presumably their ability to withstand these high temperatures has evolved by selection and adaptation Some lower forms of life like *Paramoecium* can be experimentally adapted to high temperature by gradual exposure

In warm blooded animals variations in heat sensitivity among different somatic cells are known but further investigations are needed Human spermatozoa at 37 C lose their motility and die in 24 hours and spermatogenesis fails to develop or declines in undescended testicles The brain is probably next in order of susceptibility in

Flash burns —Here the burning temperature is high but the duration of burning is very short (*see* Chapter 23) The temperature of the epidermis or even only its superficial layers may rise considerably whilst there may be only a small temperature rise in the upper dermis and perhaps none in the deeper part Necrosis in this superficial variety will be confined to the epidermis However, slight prolongation of the high temperature may permit the dermal temperature to rise considerably and this will result in a deep burn

Influence of oedema during burning —With surface burning temperatures between 55° and 60°C the equilibrium temperature at the dermis-fat junction during the steady state tends to remain constant, 50°C in the guinea-pig (Mendelssohn and Rossiter, 1944) and 48°C in the pig (Henriques and Moritz, 1947) Sevitt (1949) found that there is a rapid onset of considerable oedema associated with developing capillary stasis when the dermal temperature rises to or above 48°C in the guinea-pig, the oedema rapidly accumulated and greatly increased the thickness of the dermis Thus the appearance of relatively cool oedema fluid during the burning process counterbalances the tendency to an increase in the dermal temperature due to the uptake of heat from the external heat source The result is a constant equilibrium temperature for burns in which dermal oedema rapidly forms Sometimes the subcutaneous temperature actually falls temporarily after the initial rise and this is due to the rapid accumulation of a larger amount of oedema fluid

The effect was not seen with lower burning temperatures which did not produce oedema rapidly nor with higher burning temperatures which rapidly coagulated the dermis and the blood vessels

REFERENCES

Ashe, W F, and Roberts, L B (1945) *War Med*, **7**, 82
Henriques, F C (1947) *Arch Path*, **43**, 489
— and Moritz, A R (1947) *Amer J Path*, **23**, 531
Mendelssohn, K, and Rossiter, R J (1944) *Quart J exp Physiol*, **32**, 201
Moritz, A R (1947) *Amer J Path*, **23**, 915
— and Henriques, F C (1947) *Ibid*, **23**, 695
Sevitt, S (1949) *J Path Bact*, **61**, 427
— (1954) *Proc R Soc Med*, **47**, 225

of exposure and the question of latent injury needs to be considered

Time and temperature—All workers agree that the critical temperature at which cell death occurs depends on exposure time that exposure time for cell death depends on temperature and that these are inversely related The original observations on skin were made by Cohnheim (1873) on rabbits ears Immersion in water at 45 C for 30 minutes or at 49 for 6 minutes was without effect, but exposure to 52 C for 6 or 7 minutes produced patchy necrosis and 60 C for the same period produced complete necrosis. In the ears of mice McMaster and Hudack (1932, 1934) found that a burning iron applied at 59°C for 1 minute or at 67°C for 20 seconds produced necrosis. Histological evidence of epidermal cell death was studied by Leach Peters and Rossiter (1943) Reversible cytological changes followed the application of a burning iron at 47°C for 6 minutes and necrosis followed burning at 50 for 3 minutes and 55° for 1 minute Lower temperatures applied for longer periods also kill epidermis necrosis was produced by Moritz and Henriques (1947) after burning at 44 C for 6 *hours* The minimal temperature for necrosis is probably even lower because explants of skin fragments failed to survive in culture when the incubation was carried out at 42°C for 12 hours (Cruickshank 1956) Other cells also die at temperatures only a few degrees above that of blood heat. Chick osteoblasts are killed at temperatures between 44 and 47°C depending on the time of exposure (Pincus and Fisher, 1931) and tumour cell transplants are killed between 42° and 47°C depending on the duration of heating (Loeb 1903 Stevenson 1919)

The time–temperature relationship for *in vivo* burns is more complicated than that involved in the heating of free cells because of the gradient of temperature within the skin The relationship was studied by Moritz and Henriques (1947) using necrosis of the whole thickness of human and pig epidermis as their threshold This was produced by a burning (surface) temperature of 44 C the lowest temperature investigated in 6 hours Injury was quicker as the burning temperature rose between 44 and 51 C the relationship was linear and the time required for epidermal necrosis was halved for each rise of 1 C About 51 C the curve steepened towards the temperature axis as if the rate of injury further increased while epidermal necrosis occurred within 1 second above 70 C Below 44 C the rate of injury decreased These effects are partly related to the physics of heat transfer through the skin from the heated surface (Chapter 1) and partly to the rate of recovery of epidermal cells.

rabbits the lethal cerebral temperature is 42°–43°C (approximately 107°–109°F) Between 46° and 50°C (115° and 122°F) leucocytes are killed (Schultze, 1865) and irreversible changes occur in red cells at about 50°C In guinea-pigs the permeability of capillary endothelium increases after the dermis reaches a temperature between 41° and 45°C (106°–113°F) and irreversible capillary changes (stasis) occur after it reaches 47°–48°C (116°–118°F) (Chapter 3) The critical temperature of death for epidermal and other cells is discussed later

Nevertheless the temperature at which cell death occurs depends on the duration of exposure The time–temperature relationship may well be influenced by other environmental factors, by the age of the cells and by their degree of activity Basically the effect of hyperthermia depends on the difference between the rate of injury to protoplasm and the rate of recovery and repair

BODY HYPERTHERMIA

The body's temperature may rise to the injurious level of 42°–43°C either by its failure to lose metabolic heat or by exposure to a high environmental temperature The effects include (1) a generalized vasodilatation which may cause a relative oligaemia and peripheral circulatory failure, (2) respiratory symptoms, the first of which is polypnoea, caused by reflex stimulation of the respiratory centre, later respiratory failure may occur, and (3) possible central cardiac failure It is difficult to say which of these produces death Hartman (1937) drew an analogy between the effects of high temperature and the pathology of anoxia He found a decreased oxygen content of arterial and venous blood Some of the older workers thought that death resulted from heat inactivation of intracellular globulins (Halliburton and Mott, 1903) After the experimental exposure of pigs to temperatures found in burning buildings there was often an acute hyperpotassaemia due to release of potassium mainly from damaged red cells, and this was associated with or caused a rapidly fatal central heart failure (Moritz and his colleagues, 1947) Death occurred when the rectal temperature rose to about 42°C (107·6°F) but the blood temperature was higher Patients dying of heat-stroke show venous congestion, petechiae in the brain and mucous membranes, cloudy swelling and possibly necrosis in the liver kidneys and myocardium, swelling of the spleen and depletion of adrenocortical lipoid, delayed manifestations include pyknosis and disintegration of cortical neurones (Malamud, Haymaker and Custer, 1946)

HYPERTHERMIA OF EPIDERMAL AND OTHER CELLS

Before discussing the morphological and biochemical effects of heat on cells the interrelationship between time and temperature

macroscopic epidermal injury When the sub-threshold combination was repeated on the same site 24 and 48 minutes later epidermal necrosis occurred however when the intervals between the three burns was lengthened to 4 hours or longer necrosis of the epidermis did not develop They concluded that the sub-threshold combination inflicted a latent injury which required more than 24 minutes and less than 4 hours for recovery The recovery time lengthened as the time and temperature of exposure approached the threshold level Henriques (1947) suggested that latent injury damaged a non critical fraction of the cellular proteins which permitted partial cell function at the end of the exposure and that during the recovery period the proteins were replenished This is plausible but it does not mean that all the epidermal cells at a given level in the epidermis were equally affected Histological study by Moritz (1947) showed a focal distribution of irreversibly heat affected epidermal cells interspersed with groups of normal cells This indicates that a proportion of the epidermal-cell population was irreversibly affected by the sub-threshold injury and suggests that the proportion increases as the insult approaches the threshold level

Morphological changes.—The histocytological effects of heat on guinea pig epidermis were studied by Leach Peters and Rossiter (1943) using burning temperatures ranging from 45° to 80°C and a similar investigation on the pig was reported by Moritz (1947) The minimal sign of injury was swelling of the cytoplasm and nucleus with some loss of cytoplasmic basophilia which Leach and his colleagues considered to be reversible The appearance suggested an increased permeability of the cytoplasmic and nuclear membranes which permitted the entry of excess water and this may have been related to an increased intracellular metabolism or to a shift in *p*H between nucleus and cytoplasm Experimental warming of isolated cells (for example *Spirogyra* and *Paramoecium*) also indicates that the first physical change is often an increased permeability and swelling of the cell (Lepeschkin 1923 Port 1927) which Port believes to be reversible Similarly the swelling of red cells is the first visible effect of heat, and the earliest sign of thermal injury to capillary endothelium is an increase of its permeability

A slightly more severe injury produced the beginning of nuclear collapse or contraction with dispersion of the chromatin a more uniform staining of the nucleus and the appearance of a clear perinuclear vacuole (Leach Peters and Rossiter 1943) Moritz thought that the vacuole was at first intranuclear that the nucleus was swollen that there was a redistribution of water and solids

In the initial unsteady state of heat transfer the temperature of the skin rises steeply and progressively as the heat capacity of the skin is satisfied, whilst during the subsequent steady or equilibrium state the temperatures at various skin levels have reached their maximum and there is a balance between heat gain and heat loss Thus in prolonged "low" temperature burns the time needed to raise the temperature of the basal-cell layer is only a fraction of that necessary to produce epidermal necrosis, because the temperature of the epidermis is a steady maximum during most of the burning This accounts for the linear relationship between 44° and 51°C Above 51°C the time required to stabilize the epidermal temperature becomes relatively more and more significant as the burning time shortens Furthermore, the rate of production of injury to the cells far exceeds their rate of recovery Therefore the curve deviates from its linear relationship Below 44°C injury is produced so slowly that the rate of recovery becomes significant, and very prolonged burning is necessary before necrosis can occur

A similar explanation accounts for the time–temperature thresholds producing increased capillary permeability in experimentally-burned guinea-pig skin (Sevitt, 1954, *see also* Fig 2, page 5) This curve also shows an almost linear relationship below a temperature of 51°C and a steep deviation to the temperature axis above 52°C Curiously this curve is almost identical with that found by Moritz and Henriques (1947) for epidermal necrosis in man and pig

The time–temperature thresholds for the production of full-thickness necrosis of guinea-pig skin were investigated by Sevitt (1949) and were naturally higher than those which produced only epidermal necrosis or permeability change Temperatures of 70°, 65°, 62°, and 59°C produced full-thickness skin-loss in 10, 20, 30 and 60 seconds respectively and the relationship was exponential The thresholds were almost identical with those just producing (1) skin analgesia and (2) stasis of the blood flow in the capillaries throughout the thickness of the dermis within a few hours of burning (*see* Fig 18, page 33)

Latent injury —If the application of a burning-iron at a particular temperature for *t* seconds just produces a particular effect on the skin, it may be asked what happens to the tissue before *t* seconds is reached, is a latent or unrecognizable cellular injury inflicted by sub-threshold combinations? Using pigs, Moritz and Henriques (1947) investigated this by repeating sub-threshold burns on the same site A single burn at 49°C for 9 minutes just produced epidermal necrosis, but 49°C for 3 minutes merely produced a little erythema without

macroscopic epidermal injury When the sub-threshold combination was repeated on the same site 24 and 48 minutes later epidermal necrosis occurred however when the intervals between the three burns was lengthened to 4 hours or longer necrosis of the epidermis did not develop They concluded that the sub-threshold combination inflicted a latent injury which required more than 24 minutes and less than 4 hours for recovery The recovery time lengthened as the time and temperature of exposure approached the threshold level Henriques (1947) suggested that latent injury damaged a non critical fraction of the cellular proteins which permitted partial cell function at the end of the exposure and that during the recovery period the proteins were replenished This is plausible but it does not mean that all the epidermal cells at a given level in the epidermis were equally affected Histological study by Moritz (1947) showed a focal distribution of irreversibly heat affected epidermal cells interspersed with groups of normal cells This indicates that a proportion of the epidermal-cell population was irreversibly affected by the sub-threshold injury and suggests that the proportion increases as the insult approaches the threshold level

Morphological changes.—The histocytological effects of heat on guinea pig epidermis were studied by Leach Peters and Rossiter (1943) using burning temperatures ranging from 45° to 80°C and a similar investigation on the pig was reported by Moritz (1947) The minimal sign of injury was swelling of the cytoplasm and nucleus with some loss of cytoplasmic basophilia which Leach and his colleagues considered to be reversible The appearance suggested an increased permeability of the cytoplasmic and nuclear membranes which permitted the entry of excess water and this may have been related to an increased intracellular metabolism or to a shift in pH between nucleus and cytoplasm Experimental warming of isolated cells (for example, *Spirogyra* and *Paramoecium*) also indicates that the first physical change is often an increased permeability and swelling of the cell (Lepeschkin 1923 Port, 1927) which Port believes to be reversible Similarly the swelling of red cells is the first visible effect of heat and the earliest sign of thermal injury to capillary endothelium is an increase of its permeability

A slightly more severe injury produced the beginning of nuclear collapse or contraction with dispersion of the chromatin a more uniform staining of the nucleus and the appearance of a clear perinuclear vacuole (Leach Peters and Rossiter 1943) Moritz thought that the vacuole was at first intranuclear that the nucleus was swollen that there was a redistribution of water and solids

within the nucleus and that the effect was irreversible Mitosis was inhibited

A more severe injury produced definite evidence of irreversibility (Fig 7), namely a progressive disintegrative necrosis of the nucleus and cytoplasm Leach and his colleagues described considerable nuclear collapse, the nuclei becoming crescentic or flattened, with a large perinuclear space, the appearance of Feulgen-positive nuclear granules between the prickle cells and in the corium, and the release of pyronin-positive granules (ribonucleic acid) from the cytoplasm which lost its basophilic staining Karyorrhexis and karyolysis were progressive and by 24 hours after burning the nuclei were seen as faintly eosinophilic architectural ghosts devoid of nucleoprotein The prickle boundaries first separated from one another and from the basement membrane and many virtually disintegrated Moritz thought that nuclear rupture was the first sign of irreversible damage to the cells in the superficial and intermediate layers but that cytoplasmic eosinophilia and vacuolation was the earliest sign of necrosis in the basal-cell layer *In vitro* culture of heated fragments of skin (Cruickshank, 1956) clearly demonstrates the progressive nuclear and cytoplasmic disintegration, and the results indicate that disintegration can develop even when there is no immediate microscopic evidence of injury For example, fragments of skin from the ear of a guinea-pig were placed in saline at 50°C for 15 and 60 seconds respectively Histological examination without subsequent culture revealed normal epidermal cytology in both (Fig 3), examination after 2½ days' culture showed gross nuclear disintegration in the epidermis heated for 60 seconds (Fig 4) whilst there was a normal cytology and migration of cells of the deeper half of the epidermis which had been heated for 15 seconds Evidence from other sources also suggests that the nucleus is the most heat sensitive of all cell constituents For example, when frog cells are heated to 37°C the nuclei fragment and disappear but the cytoplasm continues to move (Ruzicka, 1918)

Heat coagulative necrosis occurs at higher temperatures and the first evidence in 1-minute burns was at 60 C (Leach Peters and Rossiter, 1943) The nuclei appeared to be preserved as if fixed but the chromatin was diffuse instead of granular (Fig 8) At higher temperatures (70° and 80°C) the coagulation was associated with nuclear distortion, flattening and elongation and with collapse of the cytoplasm (Figs 11 and 12) These effects were present immediately after burning but unlike the disintegrative process they remained subsequently unaltered

In summary the minimal to severe morphological effects of heat

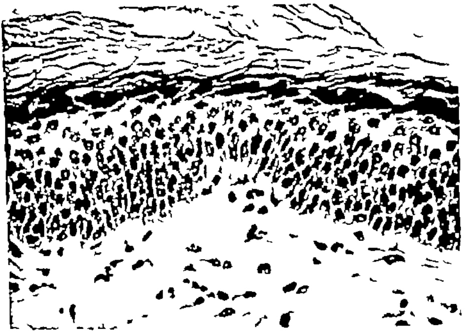


FIG. 3

FIG. 4

FIGS. 3 and 4.—Two fragments of skin from the ear of a guinea-pig were placed in saline at 50° C for 60 seconds. One was sectioned after immediate fixation in formol-saline (Fig. 3) whilst the other was "cultured" *in vitro* for 2½ days, then fixed and sectioned (Fig. 4). Fig. 3 shows that the epidermis had a normal cytology immediately after burning, and Fig. 4 that fragmentation and lysis of the nuclei took place later. (Haematoxylin and eosin × 320.) (*Figs. 3 and 4 by courtesy of Dr. C. N. D. Cruickshank.*)

within the nucleus and that the effect was irreversible. Mitosis was inhibited.

A more severe injury produced definite evidence of irreversibility (Fig. 7), namely a progressive disintegrative necrosis of the nucleus and cytoplasm. Leach and his colleagues described considerable nuclear collapse, the nuclei becoming crescentic or flattened, with a large perinuclear space, the appearance of Feulgen-positive nuclear granules between the prickle cells and in the corium, and the release of pyronin-positive granules (ribonucleic acid) from the cytoplasm which lost its basophilic staining. Karyorrhexis and karyolysis were progressive and by 24 hours after burning the nuclei were seen as faintly eosinophilic architectural ghosts devoid of nucleoprotein. The prickle boundaries first separated from one another and from the basement membrane and many virtually disintegrated. Moritz thought that nuclear rupture was the first sign of irreversible damage to the cells in the superficial and intermediate layers but that cytoplasmic eosinophilia and vacuolation was the earliest sign of necrosis in the basal-cell layer. *In vitro* culture of heated fragments of skin (Cruickshank, 1956) clearly demonstrates the progressive nuclear and cytoplasmic disintegration, and the results indicate that disintegration can develop even when there is no immediate microscopic evidence of injury. For example fragments of skin from the ear of a guinea-pig were placed in saline at 50°C for 15 and 60 seconds respectively. Histological examination without subsequent culture revealed normal epidermal cytology in both (Fig. 3), examination after 2½ days' culture showed gross nuclear disintegration in the epidermis heated for 60 seconds (Fig. 4) whilst there was a normal cytology and migration of cells of the deeper half of the epidermis which had been heated for 15 seconds. Evidence from other sources also suggests that the nucleus is the most heat sensitive of all cell constituents. For example, when frog cells are heated to 37°C the nuclei fragment and disappear but the cytoplasm continues to move (Ruzicka, 1918).

Heat coagulative necrosis occurs at higher temperatures and the first evidence in 1-minute burns was at 60°C (Leach, Peters and Rossiter, 1943). The nuclei appeared to be preserved as if fixed but the chromatin was diffuse instead of granular (Fig. 8). At higher temperatures (70° and 80°C) the coagulation was associated with nuclear distortion, flattening and elongation and with collapse of the cytoplasm (Figs. 11 and 12). These effects were present immediately after burning but unlike the disintegrative process they remained subsequently unaltered.

In summary the minimal to severe morphological effects of heat

release of protein split products not due to proteolytic action and a subsequent proteolysis probably of enzymatic origin (*see* below) The proteins released from *in vitro* heated slices of skin were also studied by Rosenthal Samet Winzler and Shkolnik (1957) who isolated a protein resembling gelatin in its electrophoretic behaviour and hydroxyproline content particularly after heating at relatively high temperatures for prolonged periods This was presumably derived from heat altered collagen Smaller amounts of other proteins were also detected including proteins containing hexose and sialic acid

Enzymes—Enzymes and protoplasm both have a temperature optimum beyond which their activity declines and their heat destruction is retarded by drying. For these and other reasons Oparin and Manskaya (1933) argued that heat inactivation of enzymes associated with protein precipitation was the mechanism of injury Studies of enzymes and of enzyme systems in tissues exposed to 50°C have shown a considerable variation in temperature sensitivity (Peters 1945) Cytochrome-oxidase malic-dehydrogenase and lactic-de hydrogenase lost most of their activity in 2 5 minutes whilst hexokin ase amino-acid oxidase cathepsin and skin proteinase were much less or hardly at all affected Of the enzyme systems studied the pyruvate-oxidase system in brain was sufficiently inactivated to account for injury Hershey and Mendle (1954) extended this work by a quantitative microchemical analysis of enzymes in normal and heated skin They found the normal human epidermis to be rich in 6-phospho-gluconic dehydrogenase purine nucleoside phosphorylase aldolase fumarase malic-dehydrogenase lactic-dehydrogenase and acid phosphatase and also contained alkaline phosphatase Scalds were made at 50°C for 5 minutes and the skin was removed 30–60 minutes after injury Comparison of scalded and normal epidermis was restricted to four enzymes aldolase 6-phospho-gluconic dehydrogenase malic-dehydrogenase and acid phosphatase No significant difference in their activity between normal and scalded skin was found Unfortunately histological changes were not re ported but the severity of burning was likely to have produced epidermal necrosis Although the enzymes studied survived the heat injury at 50 C their results do not exclude interference with other vital enzyme systems The different results on the heat stability of malic-dehydrogenase (*cf* Peters results) are of interest and may be due to the methods employed. Oxygen uptake was measured by Peters and oxalo-acetic formation by Hershey and Mendle It is possible that the decreased uptake of oxygen resulted from inter ference with later steps in oxidation

on epidermal cells are (1) reversible swelling, (2) disintegrative necrosis and (3) coagulative necrosis

Biochemical and biophysical changes Theoretically heat may affect any or all of the cell's constituents, functions and metabolic processes, and these include (1) alteration of protoplasmic proteins, (2) inactivation of enzymes and metabolic processes, (3) cellular asphyxia, (4) alterations in antigens and (5) changes in protoplasmic lipoids Unfortunately knowledge of the actual changes is meagre

Cell proteins—Morphological evidence of heat-disintegrative and coagulative necrosis of nuclear and cytoplasmic proteins has already been discussed Henriques (1947) calculated that to produce irreversible epidermal effects by burning requires an activation energy of about 150 kilocalories per mol and an entropy change of about 395 units These correspond to the energy requirements of thermal alterations of proteins (that is, heat denaturation of egg albumen requires 132 kilocalories per mol) and he concluded that death of the cells was due to thermal alteration of proteins Although the heat coagulation curves of serum albumen, egg albumen, haemoglobin, and so on, are similar to those of protoplasm, nevertheless heat denaturation and coagulation of proteins cannot fully explain the mechanism of heat injury because certain environmental factors such as narcosis can modify heat injury to living cells but not the coagulation of proteins (*see* Cameron, 1952) The relationship of irreversible protein changes short of heat coagulation to morphological and enzymatic effects and to changes at the cell surface is not known

The finding of altered proteins and protein-degradation products in the exudate, blood, lymph and urine suggests that heating breaks down and liberates various proteins in skin For example *in vivo* studies have shown that polypeptides with leukotaxic properties are present in burn exudate (Cullumbine and Rydon, 1946), that an abnormal protein was present in the lymph from the burned area of dogs (Perlmann, Glenn and Kaufman, 1943), that the glycoprotein value of the serum is raised (Keyser, 1952), that the blood and tissues are flooded with skin protein antigens (Fedorov, 1956) and that the peptide excretion in the urine is increased (Baar, 1956) Some of these findings may be explained by the complex metabolic changes which occur outside the burned area, but chemical and physical studies of skin heated *in vitro* have also demonstrated an alteration of proteins Part of this is apparently the direct result of heat injury whilst part results from subsequent enzymic activity *In vitro* studies of guinea-pig skin slices by Ungar and Damgaard (1954) showed an initial

account for epithelial cell death in burns It has been shown that one kind of full thickness loss burn is associated with capillary stasis through the whole depth of the dermis (Chapter 3) Histological examination of the skin suggests that in some of these burns the epithelial cells in the deeper parts of the follicles and sweat ducts are not irreversibly affected at first but that their death occurs later This could result from ischaemic anoxia of capillary stasis

Antigens —Like enzymes, cell antigens also show considerable variation in temperature sensitivity The activity of the Rhesus D-antigen is lost or modified when red cells are heated to between 50° and 56 C so that Rh positive cells appear to become Rh negative when a saline agglutinating anti D antiserum is used (Ponder and Ponder 1952) The heat lability of the D-antigen occasionally produces difficulty in the Rhesus typing of the blood of recently and extensively burned patients (Chapter 15) On the other hand the M antigen of red cells is relatively heat stable and only a small minority of M positive cells become inagglutinable to anti M serum after heating to similar temperatures (Lilly 1956) The soluble A and B antigens in the saliva of human secretors resist boiling so that anti A and anti B sera lose their activity when boiled saliva is added but the effect of heat on the A and B antigens in red cells does not appear to have been studied

Protoplasmic lipoids and the cell membrane —Because many lipoids alter physically at about 45°C Bělěhradek (1935) proposed that a physical change in protoplasmic fats was an early effect of heat injury Peters (1945) could not decide whether the first sign of heat injury was a change in an enzyme or damage to a lipoprotein com plex at the cell interface but thought that the latter was more likely

The increased permeability of capillary endothelium from heat (Chapter 3) may result from a change in the cell membrane perhaps in surface lipoproteins The permeability of the red cell membrane is altered when blood is heated up to 50°C and intracellular potassium is lost into the plasma, but morphological changes in the erythrocytes are not visible (McLean Moritz and Roos 1947) Above 50°C spherical microcyte fragments are budded from the surface sphero-cytosis occurs, and fragmentation and lysis of the erythrocytes develop (Figs 55 and 56—Chapter 15) Some of these changes are related to damage of the cell surface Studies of the potassium and sodium content of burned skin have shown a loss of intracellular potassium and an uptake of sodium (Fox and Baer 1947 Fox and Keston 1945 Moore Evans and Ball 1948) and these diffusion changes across the cell membrane may also be due to alterations in

A new enzyme, skin-proteinase, was discovered by Beloff and Peters (1945) which, like trypsin, was active between pH 7 and 8 and which unlike other enzymes was comparatively stable up to 70°C Burning nevertheless caused a considerable loss of the enzyme from the skin due to its liberation from the cells (Chapter 3) Proteolysis by heated skin slices was later investigated by Ungar and Damgaard (1954), who confirmed that it was largely an enzymatic process, but they concluded that heat acted by converting an inactive enzyme precursor present in normal tissue into an active proteinase

Respiration—Using a micro-respirometer Cruickshank (1956) measured the oxygen uptake in culture of excised guinea-pig skin for two hours after immersion in saline at various temperatures for 30 seconds Saline temperatures up to 50°C produced only a slight decrease in oxygen uptake, but after heating at and above 60°C oxygen uptake was slight or absent The change between 50° and 60°C was abrupt This indicates that between 50° and 60°C rapid irreversible changes affect the cellular respiration and these may be related to the heat coagulation of proteins (*see* page 12) Cruickshank also measured the oxygen uptake after immersion at 45°C and found that it depended on the duration of heating and the time elapsing after the burn Measurements at 2 hours after immersion showed a progressive fall of oxygen consumption from a relatively normal value in the skin immersed for half an hour to little or no respiration in the skin immersed for 4 hours This confirmed and extended the few observations by Manifold and Peters (*see* Peters, 1945), who found that a 6-minute application of the burning iron at 47°C did not produce a fall in oxygen consumption in pieces of skin removed from the animal Cruickshank found that when oxygen uptake was measured in culture 24 hours after immersion at 45°C the oxygen consumption had further decreased but the skin immersed for 2–3 hours now showed little or no respiratory activity This indicates that prolonged heating at a "sub-lethal" temperature produces a progressive loss of respiratory activity

Thus respiratory death after heating may be either rapid or progressive

Cellular asphyxia—It has been shown that heating of the free-living *Paramoecium* first increases its oxygen consumption and then causes death (Winterstein, 1905) It was therefore suggested that death was anoxic because the oxygen supply could not keep pace with cellular demands since warming the medium diminished its power to absorb oxygen Relative anoxia of this kind is very unlikely to cause death in vascularized tissues Nevertheless ischaemic anoxia might sometimes

account for epithelial cell death in burns It has been shown that one kind of full thickness loss burn is associated with capillary stasis through the whole depth of the dermis (Chapter 3) Histological examination of the skin suggests that in some of these burns the epithelial cells in the deeper parts of the follicles and sweat ducts are not irreversibly affected at first but that their death occurs later This could result from ischaemic anoxia of capillary stasis

Antigens—Like enzymes cell antigens also show considerable variation in temperature sensitivity The activity of the Rhesus D-antigen is lost or modified when red cells are heated to between 50 and 56 C so that Rh positive cells appear to become Rh negative when a saline agglutinating anti D antiserum is used (Ponder and Ponder 1952) The heat lability of the D antigen occasionally produces difficulty in the Rhesus typing of the blood of recently and extensively burned patients (Chapter 15) On the other hand the M antigen of red cells is relatively heat stable and only a small minority of M positive cells become inagglutinable to anti M serum after heating to similar temperatures (Lilly 1956) The soluble A and B antigens in the saliva of human secretors resist boiling so that anti A and anti B sera lose their activity when boiled saliva is added but the effect of heat on the A and B antigens in red cells does not appear to have been studied

Protoplasmic lipoids and the cell membrane—Because many lipoids alter physically at about 45 C Bělěhradek (1935) proposed that a physical change in protoplasmic fats was an early effect of heat injury Peters (1945) could not decide whether the first sign of heat injury was a change in an enzyme or damage to a lipoprotein com plex at the cell interface but thought that the latter was more likely

The increased permeability of capillary endothelium from heat (Chapter 3) may result from a change in the cell membrane perhaps in surface lipoproteins The permeability of the red cell membrane is altered when blood is heated up to 50° C and intracellular potassium is lost into the plasma, but morphological changes in the erythrocytes are not visible (McLean Moritz and Roos 1947) Above 50°C spherical microcyte fragments are budded from the surface sphero-cytosis occurs, and fragmentation and lysis of the erythrocytes develop (Figs 55 and 56—Chapter 15) Some of these changes are related to damage of the cell surface Studies of the potassium and sodium content of burned skin have shown a loss of intracellular potassium and an uptake of sodium (Fox and Baer 1947 Fox and Keston 1945 Moore Evans and Ball 1948) and these diffusion changes across the cell membrane may also be due to alterations in

lipoprotein complexes The exchange of ions is equimolecular Skin scalded at 75°C lost potassium and gained sodium in addition to extracellular water and sodium, that is the sodium gain exceeded the gain in water even when the burns were at immediate heat-coagulative temperatures of 94°–99°C tissue cell potassium was extruded and an equivalent gain of sodium occurred before there was significant accumulation of local fluid (Fox and Baer, 1947) Moore, Evans and Ball (1948) concluded that the entrance of sodium into skin cells is evidence of cell death, but this is unlikely unless the diffusion is free like that across a lifeless membrane.

On the other hand Henriques (1947) pointed out that the activation energies of biophysical processes like the melting of fats and changes in viscosity, rigidity, diffusion and tensile strength are very low, and therefore the rate of injury above the threshold level would be linear with rise in temperature He concluded that the irreversible changes at higher temperatures, which required high activation energies and at which a linear time–temperature relationship did not exist, could not result from a physical change in cell lipoids although such changes might account for the effects produced on the epidermis at the lower temperature range (45°–50°C)

It may be concluded that heat can produce cell death by interfering with one or more vital cellular processes, and that the functions and cellular structures affected depend on the nature of the cell, the temperature applied, its duration and other environmental factors Disturbances of the cell membrane, of one or more key enzymes or irreversible protein changes all appear to play a part under different conditions

HISTOLOGICAL CHANGES IN BURNED SKIN

Accounts of the histology of burned skin are few but date back before Unna's description in 1896 These have been mainly concerned with descriptions of blister formation and of heat-coagulative changes in accidental human burns or in severe burns produced experimentally on animals

In the following account the changes described in human skin are based on a histological (biopsy) study of accidental human burns in many of which the depth of necrosis determined histologically was checked by the subsequent clinical course of the burn

EPIDERMAL CHANGES

The stratum corneum is often loosened into its component layers and this probably results from the expansion of the keratin and its temporary transformation into a semiplastic material The effects of

heat on human epidermal cells (Figs 7 to 12) are in all essentials similar to those described by Leach Peters and Rossiter (1943) for guinea pig skin (*see pages* 11–12) Sometimes there is a horizontal gradation of changes in the epidermis extending for several millimetres at the edge of the burn but often the zone of disintegrative necrosis is small or absent and the junction between viable and heat coagulated epidermis is fairly sharp (Fig 9)

Superficial burns may be defined histologically as those in which the deeper part of the epidermis particularly the basal-cell layer remains viable and is not irreversibly affected either by disintegrative necrosis or by heat coagulation In partial skin loss burns the whole epidermis suffers irreversible changes and a variable but incomplete depth of the dermis is always affected

Vesication.—Unlike the skin of most animals human skin blisters readily probably because the superficial capillary network of the dermis is highly developed and has intimate ramifications in the subepidermal papillae whilst in animals the superficial plexus is less developed The blister fluid exudes from the superficial capillaries and collects below the epidermis (Fig. 5) because the cementing membrane between dermis and epidermis has been destroyed A more superficial separation within the epidermis may occur in areas like the palms and soles where the epidermis is thick (Patey and Scarff 1944–45) but it is unusual

Histologically incipient blistering is manifest by small spaces containing an eosinophilic exudate between a few basal cells and the dermis and perhaps rupturing between basal cells and the adjacent prickle cells. The epidermal roof of blisters is usually but not invariably heat necrotic Sometimes the deep epidermal cells are viable in burns which result in epidermo-dermal loosening. Vesication would then produce *secondary* epidermal necrosis In sections the blister fluid appears as an eosinophilic albuminous exudate containing numbers of polymorphs and often strands of fibrin (Fig 5)

Blistering is not diagnostic of partial skin loss burns as it may occur in certain kinds of full thickness burns such as deep scalds

Dermo-epidermal loosening or separation may occur in burns of the guinea pig rabbit, pig or other animals The anchoring basement membrane disappears as if it had been destroyed or digested The junction between the epidermis and dermis may be moist but the amount of fluid present is never enough to raise a blister Leach Peters and Rossiter (1943) noticed this in guinea pig burns after applying the burning iron at 60–65 C for 1 minute and Moritz (1947) found it in burns of the pig at temperatures above 49 C

FIG 5 —Histology of a burn blister removed 2 days after burning The whole thickness of the epidermis has been raised by a structureless eosinophilic exudate containing a coarse network of fibrin and a loose collection of leucocytes (Haematoxylin and eosin, × 30)

It has been postulated that the cementing membrane disappears because it is digested by the uncontrolled activity of skin proteinase on its way from the heat-injured epidermis to the dermis (Beloff and Peters, 1945) This is plausible because Medawar (1941) found that treating slices of human skin with trypsin sharply separated the epidermis from the dermis and he thought that this was due to digestion of the elastin

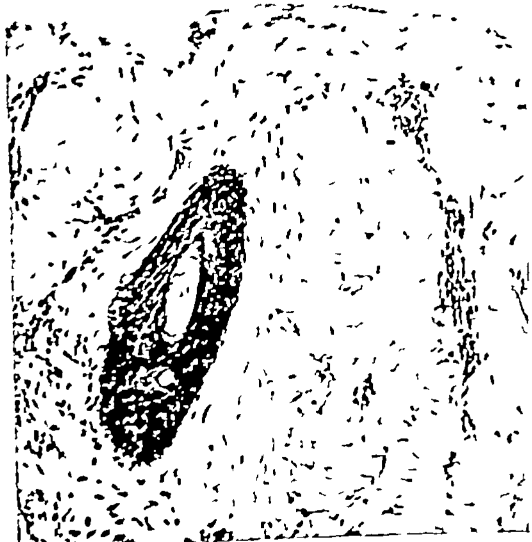


FIG 6 —Superficial partial skin-loss burn The epidermis had blistered and is absent, the dermal capillary plexus is prominent and a few leucocytes have migrated into the skin However, the hair follicle and dermal collagen are normal Biopsy, day of burning (Haematoxylin and eosin, × 120)

FIG 7

FIG 8

FIG 8 —Coagulation-necrosis of the epidermis The nuclei are preserved but hyperchromatic, their chromatin is diffuse and many are pyknotic Burn of forearm excised same day (Haematoxylin and eosin 410)

FIG 7 —Disintegrative necrosis of the epidermis Note the fragmentation deformity and disappearance of many nuclei Skin of finger excised 10 hours after burning (Haematoxylin and eosin 450)

DERMAL CHANGES

The dermis is affected in all burns which produce primary heat necrosis of the whole epidermis or which blister the skin The depth to which the dermis is involved and the quality of changes depend on the surface temperature and duration of burning in general prolonged burns are deeper and the higher temperature burns produce necrosis. In many biopsies of skin the epidermis is absent, the dermal papillae are exposed and are often flattened particularly in severe burns Many biopsies show a vertical gradient of changes the severest effects are near the surface the deep dermis is least affected and the middle zone changes are intermediate in severity

Dermal epithelium.—The gradient of epithelial damage in partial skin loss burns affects the sheaths of the hair follicles (Fig 10) the sebaceous glands and sweat ducts Few sweat coils are affected because they are deeply placed The vertical gradient from the surface

FIG 9—Horizontal gradation of the effect of heat on the epidermis at the edge of a burn Note the hyperchromatic collapsed nuclei with perinuclear vacuoles in the transition zone between heat-coagulated distorted nuclei and the viable epithelium (Haematoxylin and eosin, × 190)

downwards may be heat coagulation, heat disintegration, reversible cellular changes and normal epithelium, but usually the zone of disintegration is limited and there is a relatively sharp border between heat-coagulated and relatively normal epithelium In less severe burns necrosis may be restricted to the mouths of the follicles and ducts whilst the major depth of this epithelium may show little or no evidence of heat injury The depth of the skin loss depends upon the depth to which dermal epithelial necrosis extends Histologically a full-thickness skin-loss burn is one in which irreversible changes involve all the dermal epithelial elements

In addition to the histological signs of necrosis previously described other evidence of irreversibility are rupture of the fatty cells of the sebaceous glands, distortion of the sheaths of the hair shafts, the presence of small rents and fissures in the epithelium of the follicles

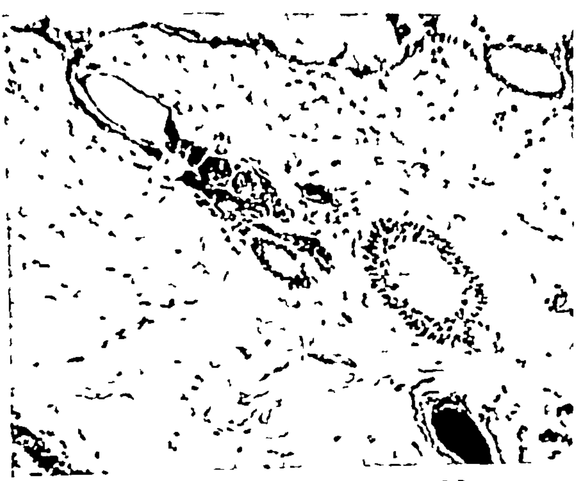


FIG 10—Guinea-pig skin showing vertical gradient of heat effect in a hair follicle Burning iron at 60 C applied for 10 seconds—biopsy excised 12 minutes later (Haematoxylin and eosin, × 100)

(Fig 14) sometimes in sweat ducts and cytoplasmic eosinophilia Heat-coagulated nuclei are often greatly elongated and distorted and their outlines may not be sharp Karyolysis, karyorrhexis or pyknosis may be present Nuclear lysis most commonly affects sweat coils (Fig. 13) The lumina of seriously injured sweat ducts are often narrowed or even absent and the ducts may appear as dark syncytial like lumenless cylinders with elongated, hyperchromatic palisading nuclei the chromatin of which may diffuse into and darken the cytoplasm (Fig. 11)

In some burns the cytological evidence of injury to the deeper epithelial elements is slight perhaps confined to nuclear swelling or slight nuclear collapse and some loss of cytoplasmic basophilia It may be difficult to decide whether the changes are reversible or likely to have progressed as disintegrative necrosis In other words, should the biopsy be classified as a deep partial skin loss burn or as a full thickness loss burn? The difficulty arises when the biopsy has been removed within a few hours of burning, at a time when nuclear and cellular disintegration may have subsequently developed Similar histological criteria in biopsies excised more than 24 hours after burning may be safely regarded as evidence of a partial skin loss injury

Collagen.—Irreversible changes in collagen are also of two kinds coagulation and a pseudo-elastotic degeneration or denaturation in which the fibres come to resemble elastic fibres (Fig. 34) The depth to which collagen is coagulated generally corresponds to the depth of the heat-coagulated epithelium. The collagen fibres are swollen into strap-like bands (Fig. 11) and in higher temperature burns they may be closely packed or almost fused into solid masses (Fig. 12) They lose their affinity for acidic dyes like eosin and fuchsin partly or completely and stain readily with basic dyes like haema toxylin methyl violet carmine and orcein Coagulated collagen is resistant to lysis from leucocytic or bacterial activity cannot be organized and will later slough from the surface Pseudo-elastotic injury is less than coagulation It may be found at the surface when coagulative changes are slight or absent or it may involve a layer of collagen deep to the coagulated zone It may correspond to the disintegrative necrosis of epithelium and of other cells and cellular structures like fibrocytes and blood vessels In biopsies excised within 24 or even 48 hours of burning the affected fibres are difficult to distinguish from normal collagen but the changes become evident later The fibres are not swollen and are eosinophilic but they have a sharp semi refractile appearance not unlike elastic fibres Many are

FIG 11 —Whole skin-loss burn excised on day of burning The epidermis is heat coagulated, the nuclei are preserved, their chromatin is diffuse but many are distorted and some elongated to spindles A sweat duct appears as a dark, apparently solid and lumenless streak and its nuclei are grossly elongated and closely packed Much of the collagen has coarsened into strap-like bands and many of the fibrocyte nuclei are hooked or bent (Haematoxylin and eosin, × 90)

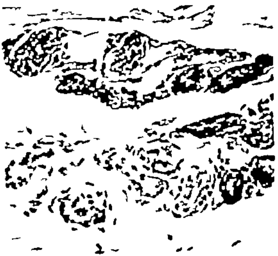
FIG 12 —Whole skin-loss burn excised day of burning The epidermis and dermis are heat coagulated and the bands of collagen are very broad and appear to have fused in many places This is the result of a higher temperature than the burn in Fig 11 (Haematoxylin and eosin × 115)

invaded by leucocytes, broken up and appear in the surface exudate (Fig 34), whilst others may be incorporated into the new dermis and presumably gradually absorbed at a later date

Fibrocytes —Necrosis of fibrocytes may also be disintegrative or coagulative The former usually culminates in nuclear lysis whilst coagulated nuclei take on bizarre irregular shapes and may be bent, hooked, rod-shaped or elongated

Blood vessels —In superficial burns, the vessels particularly of the superficial capillary plexus are hyperaemic, but although they are histologically prominent (Fig 6) many are not dilated with blood,

Fig 13.—Burn on dorsum of hand. The sweat coil appears dark because of nuclear lysis and diffusion of chromatin into the cytoplasm. Slight nuclear fragmentation also present. (Haematoxylin and eosin × 200.)



presumably because the vessels contracted after excision of the skin. When congestion is seen, the capillary endothelium is swollen and the cells are a little loosened. Numbers of red cells may be found free nearby having escaped by diapedesis. Their breakdown to haemosiderin may contribute to the brown discoloration of recently healed superficial burns. Slowing of the capillary flow may be diagnosed when congested vessels contain excessive numbers of polymorphs, most of which are lying close to the endothelial walls. Similar changes in the deeper capillaries will be seen when the injury is deeper but is short of coagulation or stasis.

Stagnation and stasis of the capillary flow may be difficult to distinguish histologically from those described above because it is a functional disorder. Characteristically many capillaries and venules

Fig 14.—Skin of arm excised 5 hours after burning. Fine fissures and rents in a hair follicle indicate irreversible damage. (Haematoxylin and eosin × 195.)

are dilated, capillary loops are often elongated and are plugged tight with closely packed red cells (Fig 16) At first these retain their normal outlines, but later they may fuse, become necrotic and appear as eosinophilic pseudo-thrombi True thrombosis may follow and also affect larger veins Karyolysis and karyorrhexis may affect the capillary endothelium and it may be difficult to decide whether this necrosis is a primary heat effect or secondary to the stasis Capillary stasis may be confined to the superficial dermis, it may extend through the whole depth of the dermis or it may be present deep to a heat-coagulated area In one kind of full-thickness skin-loss burn deep capillary stasis is at first associated with histologically viable sweat coils which later suffer lytic changes The necrosis may then be ischaemic in kind and secondary to the stasis

Heat-coagulated capillaries become converted into solid cellular streaks

Oedema.—Oedema increases the depth of the dermis but histologically it is not always readily recognizable Separation of the fibres of the arrector pili muscles is due to oedema and the collagen bundles may also be separated Fibrin is not seen within the dermis

Polymorphonuclear leucocytes.—Unlike acute inflammation from pyogenic bacteria, migration of polymorphs is not a characteristic feature of acute burn inflammation Numbers of leucocytes may be found in the dermis within a few hours of injury but they are never numerous at this time Of course leucocytic migration cannot occur when the dermal capillaries are rapidly destroyed by the burning or when they quickly become plugged and blocked by red cells, but numbers of polymorphs may continue to migrate from vessels in the less injured deeper part of the skin This probably accounts for the larger numbers of leucocytes seen in the deeper stratum reticulare in many biopsies Excess of leucocytes may also be found in the adjacent unburned area By 24–72 hours after burning many polymorphs will have migrated into areas of disintegrative necrosis such as the border between heat-coagulated skin and the deeper viable part Bacterial infection of the skin may increase the invasion of leucocytes but this usually happens after the acute aseptic inflammatory stage

REFERENCES

Baar, S (1956) *J clin Path*, 9, 144

Bělěhrádek, J (1935) "Temperature and Living Matter", *Protoplasma-Monogr Berl*, 8, 8

Beloff, A, and Peters, R A (1945) *J Physiol*, 103, 461

Cameron, G R (1952) *Pathology of the Cell* Edinburgh, Oliver & Boyd

Cohnheim, J (1873) *Neue Untersuchungen uber die Entzundung* Berlin, Hirschwald

Cruickshank, C N D (1956) Personal communication.
Cullumbine H and Rydon, H N (1946) *Brit J exp Path* 28 33
Fedorov N A (1956) *Proc 6th Cong Internat Soc Blood Tr* 44
Fox, C L, and Keston, A S (1945) *Surg Gynec Obstet* 80 561
— and Baer H (1947) *Amer J Physiol* 151 155
Halliburton, W D, and Mott F W (1903) *Arch Neurol* 2, 727
Hartman, F W (1937) *J Amer med Ass* 109 2116
Henriques, F C (1947) *Arch Path* 43 489
Hershey F B and Mendle B J (1954) *Surg Forum* 5 745
Keyser J W (1952). *J clin Path*, 5, 194
Leach, E. H., Peters, R A. and Rossiter R J (1943) *Quart J exp Physiol* 32, 67
Lepeschkin, W W (1923) *Stud Pl physiol Lab Charles Univ* 1 5 (Quoted by Cameron 1952.)
Lilly H A. (1956) *J Med Lab Technol* 13 401
Loeb L. (1903) *Virchows Arch* 172, 345
McLean, R., Moritz, A R and Roos, A (1947) *J clin Invest* 26, 497
McMaster P D, and Hudack S S (1932) *J exp Med* 56 239
— — (1934) *Ibid* 60, 479
Malamud N., Haymaker W and Custer R P (1946) *Milit Surg* 99 397
Medawar P B (1941) *Nature Lond* 148, 783
Moore, F D., Evans, R E and Ball M R (1948) *Ann Surg* 128, 266
Moritz, A. R. (1947) *Amer J Path* 23, 915
— and Henriques, F C (1947) *Ibid* 23, 695
— — Dutra F R., and Weisiger J R (1947) *Arch Path* 43 466.
Oparin, A. and Manskaya, S (1933). *Biochem. Z* 256, 190
Patey D H., and Scarff R W (1944–45) *Brit J Surg* 32, 32
Perlmann, G E. Glenn, W W L. and Kaufman D (1943) *J clin Invest* 22, 627
Peters, R. A. (1945) *Brit med Bull* 3, 81
Pincus, G., and Fisher A (1931) *J exp Med* 54, 323
Ponder R. and Ponder E. (1952) *Nature Lond* 170 928
Port, J (1927) *Protoplasma* 2, 401
Rosenthal, S R. Samet, C Winzler R J and Shkolnik S (1957) *J clin Invest* 36, 38
Ruzicka, (1918) Quoted by Cameron (1952)
Schultze, M (1865) *Arch mikr Anat* 1 1 (Quoted by Leach Peters and Rossiter 1943)
Sevitt, S (1949) *J Path Bact* 61 427
— (1954) *Proc R Soc Med* 47 225
Stevenson, H (1919) *J Cancer Res* 4, 54
Ungar G and Damgaard, E. (1954) *Proc Soc exp Biol Med* 87 378
Unna, P G (1896) *Histopathology of the Diseases of the Skin* Edinburgh Clay
Winterstein, H (1905) *Z allg Physiol* 5, 323

CHAPTER 3

ACUTE INFLAMMATORY CHANGES IN BURNED SKIN

GALEN (*circa* 130–210 A D) knew that heat could cause inflammation, and although the local circulatory changes were first investigated by Hastings (1820) it was not until the classical work of Cohnheim (1873) that the relationship of the vascular changes to fluid exudation and leucocytic migration was understood Whilst studying the minute vessels in the rabbit's ear after immersion in warm water he found that the blood flow first quickened and then slowed, fluid exuded into the tissue spaces and leucocytes became pavemented When the water was hot the blood flow became very slow and finally static

Subsequent studies have extended Cohnheim's observations The first effect of heat may be immediate blanching from contraction of the skin capillaries, but this does not always occur and seems to follow surface temperatures above 60°C If the superficial dermis is simultaneously coagulated the burned surface remains white and subsequent inflammatory changes affect only the more deeply situated vessels Otherwise the blanching passes off within a minute or so, the area reddens due to dilatation of the capillaries, the arterioles also dilate, the blood flow through the affected area quickens and the local skin temperature rises 1°–2°C The erythema is often the first visible sign of burning

Later the capillary blood flow slows, the erythema may become slightly cyanotic from reduction of haemoglobin, diapedesis of red cells takes place and pavementing of the capillary wall by leucocytes occurs This process is associated with a leakage of fluid from the capillaries which produces skin oedema In severe burns the leakage is rapid, oedema accumulates quickly, the red cells in the capillary flow slow more, and the flow may stagnate and finally become static

Leucocytic migration occurs but is usually delayed for hours and is not a characteristic feature of burning during the early inflammatory stage

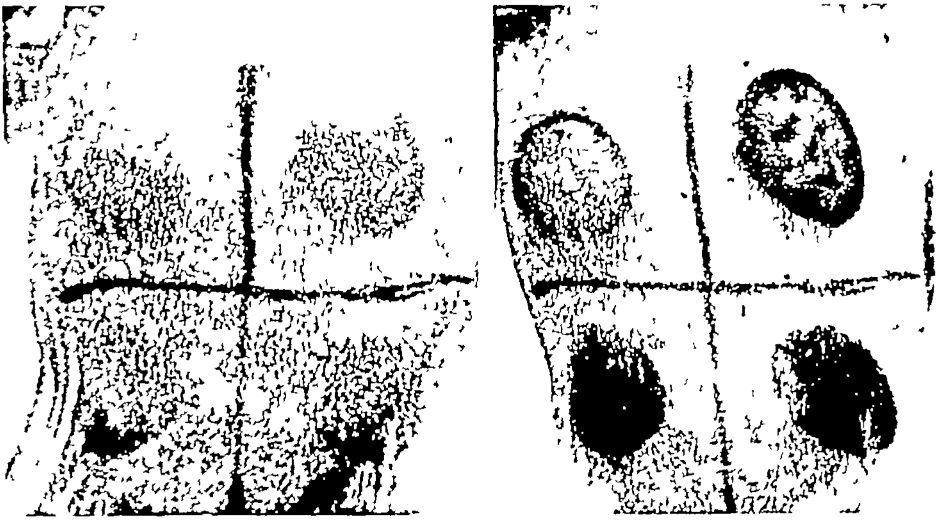
CAPILLARY PERMEABILITY

Physiological considerations —The normal mechanism governing the formation and reabsorption of tissue fluid requires brief considera-

tion The work of Starling Landis and others (see Landis 1936 1937) has shown that some fluid containing a little protein normally leaves the arterial end of the capillary enters the tissue spaces and is reabsorbed into the circulation partly through the venous end of the capillary and partly by lymphatic drainage This exit and re-entry depends (1) on a greater hydrostatic pressure at the arterial end than at the venous end of the capillary (about 30 and 20 mm Hg respectively) (2) on the colloid osmotic pressure of the capillary plasma being greater than that of the tissue fluid (about 24 and 4 mm Hg) this difference is maintained by (3) the relative *impermeability* of normal capillary endothelium to plasma proteins and (4) to a lesser extent on the tissue pressure normally about 1–3 mm Hg At the arterial end of the capillary the hydrostatic pressure (30 mm Hg) is greater than the colloid osmotic pressure difference (between capillary plasma and tissue fluid) plus the tissue pressure (24 − 4 + say 2 = 22 mm Hg) At the venous end the colloid osmotic pressure difference plus the tissue pressure (22 mm) is greater than the hydrostatic pressure (20 mm) Hence fluid leaves the capillary at the arterial end and some will return at the venous end The remainder is collected by lymph vessels.

Increased permeability —One of the most important effects of burning is the local development of an abnormal capillary permeability which allows a protein rich fluid to escape into the tissue spaces. This virtually abolishes the colloid osmotic pressure difference between the capillary plasma and tissue fluid exudate The effect is augmented by a rise of intracapillary pressure associated with capillary dilatation and increased blood flow The increased permeability of the skin vessels has been experimentally studied by dyeing the plasma with Evans blue brilliant vital red kiton fast green or trypan blue all of which combine with the plasma proteins, particularly with albumen Colouring of the burned skin is due to leakage of the dyed plasma protein and indicates a considerable increase of dermal capillary permeability (Sevitt, 1949*a*) (Fig 15) Using radioactive colloids, Cope and Moore (1944) showed that the capillaries in burned skin of dogs became almost as permeable to colloids as normal capillaries are to ions After intravenous injection the radioactivity of the lymph from the burned leg rose abruptly and reached equilibrium with the radioactivity of the plasma

Minimal permeability increasing temperature —The lowest combinations of burning temperature and time which just produce a staining of the burned skin from circulating plasma bound dye were investigated after injecting Evans blue (Sevitt 1954) The time–temperature



(*a*) (*b*)

FIG 15 —Demonstration of capillary permeability, continuation of dermal blood flow, stagnation and stasis in experimental guinea-pig burns by the double-dye technique The animal's abdomen was pencilled into quadrants and four burns at 60°C for $\begin{array}{c|c}60&30\\\hline 20&15\end{array}$ seconds were inflicted Brilliant vital red dye was then injected intracardially

(*a*) Red dyed patches corresponding to the burns appear 1 hour later They indicate the continuance of a dermal blood-flow through capillaries which have allowed plasma-bound dye to escape

(*b*) Four hours after burning, Evans blue was injected intracardially The red-dyed patches of the lower two burns have been replaced by dark blue ones, indicating the persistence of dermal blood flow and excessive capillary permeability at 4 hours after burning In the top-left burn (60 seconds) a blue ring of graded vascular damage has appeared at the periphery of the red-dyed burn indicating that stasis of the capillary blood flow had developed in the latter In the top-right burn (30 seconds) the peripheral blue ring is present but blue dye slowly invades the red-dyed area This indicates retardation or stagnation of the dermal blood flow

curve is exponential (Fig 2, Chapter 1) From this curve and from a correlation with the temperatures reached in the subdermis during burning, a *threshold* temperature was determined at and above which skin capillaries leak abnormally For guinea-pig skin this is between 41° and 45°C In man immersion of the skin in water at 38°–40°C merely produces a slight reddening, but if the temperature is increased to 43°–45°C the skin becomes bright red (Lewis, 1927) Prolonged burns at 44°–45°C produce blistering in man (Moritz and Henriques, 1947) and this rise of temperature doubles the filtration of fluid from the skin capillaries (Landis and Gibbon, 1933) Thus the capillaries in human and animal skin are very sensitive to small increases in temperature They first dilate and then become permeable when the

temperature is raised merely a few degrees above that of the body temperature

Superficial and deep permeability change.—The increased permeability may affect capillaries at different skin levels. Skin has three inter anastomosing capillary networks the superficial one is situated in the papillary layer of the dermis, a deeper plexus is related to sweat coils and the roots of hair follicles and the deepest is situated in the subdermis and subcutaneous fat. Burning of animals injected with trypan blue showed that in slight burns the dye exuded only from the superficial capillary plexus with increasing severity of burning the permeability increase affected the capillary bed of the deeper dermis and in more severe burns the deep blue colour rapidly appeared in the subcutaneous tissue (Ham, 1944)

Delayed increase in permeability.—A *delayed* increase in capillary permeability also occurs in burned skin and is most easily demonstrated in the dermal capillaries following minor burns, that is those just capable of increasing capillary permeability (Sevitt 1954) When Evans blue was introduced *before* burning, the dye did not appear in the skin for 30–60 minutes or longer although the burn became erythematous whilst if the dye was injected say 30–60 minutes *after* burning the burned area was coloured within a few minutes. In burns of a more severe nature the delayed effect is detectable in the deep subcutaneous capillaries and then it is sometimes associated with an increase in oedema developing hours after burning (*see below*)

Increase of capillary permeability is therefore of two kinds, immediate and delayed Although the delayed effect is found in capillaries which are further away from the skin surface than those which react immediately after burning, it may also take place in more superficially placed already affected capillaries unless of course they are already maximally affected

Cessation of leakage.—Loss of fluid from heat affected capillaries may continue up to 24–48 hours or sometimes longer It will continue until either (1) the capillary endothelium returns to normal when the permeability effect is reversible or (2) the tissue pressure rises and equals that of the capillary hydrostatic pressure when filtration will cease or (3) stasis of the capillary blood flow occurs or (4) through all these mechanisms acting in different layers of the affected skin possibly at different times

CAPILLARY STASIS

In severe burns (short of heat necrosis) the capillary endothelium is severely affected The capillaries exude fluid rapidly and the

erythrocytes flowing along the minute vessels become more and more concentrated As a consequence the capillary resistance increases and the blood flow becomes grossly retarded or *stagnant* This commonly ends in cessation or *stasis* of the blood flow associated with blockage of the minute vessels by tightly packed masses of red cells Histological examination of such skin shows the capillaries to be dilated and tightly packed with blood corpuscles (Fig 16) These appear normal if the skin is excised soon after the onset of stasis, but if excision is delayed, confluent intravascular eosinophilic masses,

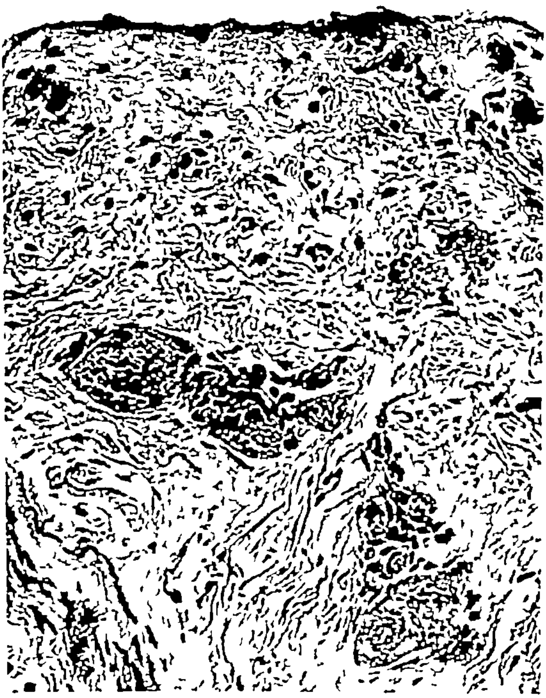


FIG 16—Capillary stasis in the dermis The capillaries are distended and closely packed with erythrocytes (Haematoxylin and eosin, × 200)

sometimes wrongly interpreted as thrombi, are seen These are not true thrombi but are blood-cell clumps undergoing necrosis, this being part of the general necrobiotic change occurring in the area affected by stasis (Kreyberg, 1949)

Time of onset of stasis and severity of burning—In experimental animals continuation of the dermal blood flow or the development of stasis can be demonstrated by injecting Evans blue or other dyes at different times *after* burning, and an elaboration of this technique is to inject different-coloured dyes at different intervals (Sevitt, 1949*a*) If stasis has occurred dye cannot enter the burned erythematous area but a narrow coloured rim due to graded vascular damage

appears around the edge of the burn (Fig 15*b*) but when blood continues to flow through excessively permeable capillaries the whole burned area becomes coloured by the dye (Fig. 15*a* and *b*) By this means stasis has been shown to develop hours minutes or seconds after burning, the interval decreasing as the severity of burning increases until stasis develops within the burning period The lowest combinations of temperature and duration of burning which produce

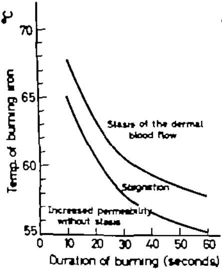


FIG 17 —Experimental guinea-pig burns. The upper curve shows the minimal time–temperature combinations of burning which just produce stasis throughout the skin (as shown by the dye technique) and the lower curve shows the maximal combinations which produce an increased capillary permeability without subsequent capillary stasis Stagnation of the dermal capillary blood flow develops in burns of intermediate severity

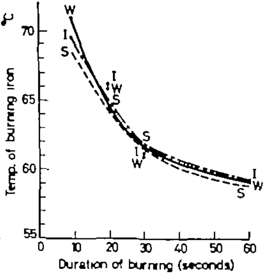


FIG 18 —Experimental guinea-pig burns. The three curves show the minimal temperatures and times of burning which just produce (1) capillary stasis in the thickness of the skin within 4 hours of burning (SS) (2) analgesia of the skin (II) and (3) subsequent whole skin loss (WW) The curves are strikingly similar and may be considered identical.

stasis in guinea pig dermis up to 4 hours after burning, and the highest combinations which just fail to produce stasis or stagnation of the dermal blood flow are shown in Fig 17 These curves are exponential

Threshold temperature —Correlation of the minimal temperature for burns of known duration which just produce stasis (upper curve Fig 17) with the experimentally determined maximal temperature in the subdermis during the burning showed that the latter was about 47–48 C in the guinea pig At and above this *threshold* temperature

erythrocytes flowing along the minute vessels become more and more concentrated As a consequence the capillary resistance increases and the blood flow becomes grossly retarded or *stagnant* This commonly ends in cessation or *stasis* of the blood flow associated with blockage of the minute vessels by tightly packed masses of red cells Histological examination of such skin shows the capillaries to be dilated and tightly packed with blood corpuscles (Fig 16) These appear normal if the skin is excised soon after the onset of stasis, but if excision is delayed, confluent intravascular eosinophilic masses,

FIG 16—Capillary stasis in the dermis The capillaries are distended and closely packed with erythrocytes (Haematoxylin and eosin, × 200)

sometimes wrongly interpreted as thrombi, are seen These are not true thrombi but are blood-cell clumps undergoing necrosis, this being part of the general necrobiotic change occurring in the area affected by stasis (Kreyberg, 1949)

Time of onset of stasis and severity of burning—In experimental animals continuation of the dermal blood flow or the development of stasis can be demonstrated by injecting Evans blue or other dyes at different times *after* burning, and an elaboration of this technique is to inject different-coloured dyes at different intervals (Sevitt, 1949*a*) If stasis has occurred dye cannot enter the burned erythematous area but a narrow coloured rim due to graded vascular damage

fluid increases locally and oedema develops The development of stagnation of the capillary blood flow bears a close relationship to the development of oedema or rather the rapid leakage of fluid causing the oedema also results in concentration of the capillary blood and hence stagnation of the flow (Sevitt 1949a)

The fluid may escape superficially and blister the epidermis and it may collect subcutaneously In man surface loss is common because the skin has a well-developed superficial capillary bed which is intimately related to the subepidermal papillae In extensive scalds the dressings and the bed may be soaked by litres of fluid When the skin surface is coagulated fluid cannot escape superficially it then *collects* in the subcutaneous tissue because the dermis is dense relatively thin and cannot hold more than a limited quantity of exudate

Fluid will leak subcutaneously if the subcutaneous capillaries are heated to the threshold temperature and in severe burns subcutaneous oedema forms rapidly and capillary stasis develops In less severe burns subcutaneous exudation may commence hours after burning as a result of a delayed permeability change

Subcutaneous oedema can be locally displaced by pressure will gravitate to dependent parts and is able to track well beyond the burned area.

Factors influencing oedema —The rate of formation of oedema and the volume present at any one time depend *inter alia* on the time since burning, the area burned and the temperature and duration of the burning itself In moderate or severe burns oedema forms rapidly and as much as 50 per cent of the fluid may accumulate within an hour (Underhill Kapsinow and Fisk 1930 Blalock 1931 Harkins 1934 1935 Leach Peters and Rossiter 1943) Underhill estimated that the oedema volume in a burn involving one sixth of the body area of rabbits was 70 per cent of the plasma volume

The severity of burning is important (Leach Peters and Rossiter 1943 Sevitt 1957) As is shown in Fig 19 burning at 60 C for 5 seconds produced little or no increase in the water content of guinea pig skin oedema developed in 10-second burns and was maximal in the 30-second and 60-second burns In the last mentioned after 1 hour the water content of the skin and subcutaneous tissue was nearly three times normal by 4 hours oedema was maximal and the water content was three to four times normal If such a burn involved one sixth of the body area the oedema volume would amount to 70–100 per cent of the animal s plasma volume Even 30 hours after burning, gross oedema was present but it is probable that most of

stasis of the dermal blood flow will develop, that is the dermis must reach a temperature above 47°–48°C during burning before stasis can occur A similar possibly lower threshold temperature must exist for human skin Many combinations of burning (surface) temperature and duration of burning will just produce the threshold temperature in perhaps different levels of the dermis

Stasis in human burns—Capillary stasis is commonly found in accidental human burns (Fig 24*b*, intermediate zone) and may set in rapidly It may also set in more slowly than in guinea-pig burns For example, it is not uncommon for the erythema of a scald to blanche on pressure or stroking for up to 24 hours after burning or even longer afterwards the erythema may fail to blanche The capillary stasis may extend through the whole depth of the dermis but is often restricted to the superficial capillary plexus

The importance of stasis.—Stasis is important in burns for three reasons First, it is irreversible, and the area affected will die and slough (Kreyberg and Vermes, 1946, Sevitt, 1949a) When the capillaries in the deepest part of the dermis are affected the most deeply situated sweat coils and hair follicles will become necrotic if not already so and full-thickness loss of the skin will follow On the other hand, although extreme retardation or stagnation of the dermal blood flow usually ends in stasis, sometimes stasis does not develop through the whole depth of the skin, the flow in the deep dermis may return to normal and then epithelialization, from deep sweat ducts for example, is possible

One kind of the full-thickness-loss burn is associated with stasis in the dermis Histological examination suggests that the deeper parts of the sweat ducts and follicles in *some* of these burns may be viable at an early stage and that only later do they become necrotic If stasis could be prevented, necrosis might be avoided and epithelial regeneration might occur This potential transformation of a whole-skin-loss to a partial-skin-loss burn requires further study

Secondly, stasis is important because the oedema becomes physiologically isolated from the capillary bed from which it originated this reduces the area for fluid reabsorption and prolongs the oedema

Thirdly, stasis is of importance because in extensive burns a significant part of the red cell volume is trapped in the engorged capillaries and is permanently lost to the circulation For this reason stasis contributes to the acute anaemia of burns (*see* Chapter 15)

OEDEMA

Local oedema is the most characteristic feature of burning When the rate of exudation from the capillaries exceeds the rate of return,

fluid increases locally and oedema develops The development of stagnation of the capillary blood flow bears a close relationship to the development of oedema or rather the rapid leakage of fluid causing the oedema also results in concentration of the capillary blood and hence stagnation of the flow (Sevitt 1949a)

The fluid may escape superficially and blister the epidermis and it may collect subcutaneously In man surface loss is common because the skin has a well-developed superficial capillary bed which is intimately related to the subepidermal papillae In extensive scalds the dressings and the bed may be soaked by litres of fluid When the skin surface is coagulated fluid cannot escape superficially it then *collects* in the subcutaneous tissue because the dermis is dense relatively thin and cannot hold more than a limited quantity of exudate

Fluid will leak subcutaneously if the subcutaneous capillaries are heated to the threshold temperature and in severe burns subcutaneous oedema forms rapidly and capillary stasis develops In less severe burns subcutaneous exudation may commence hours after burning as a result of a delayed permeability change

Subcutaneous oedema can be locally displaced by pressure, will gravitate to dependent parts and is able to track well beyond the burned area.

Factors influencing oedema.—The rate of formation of oedema and the volume present at any one time depend *inter alia* on the time since burning, the area burned and the temperature and duration of the burning itself In moderate or severe burns oedema forms rapidly and as much as 50 per cent of the fluid may accumulate within an hour (Underhill, Kapsinow and Fisk 1930 Blalock, 1931 Harkins, 1934 1935 Leach Peters and Rossiter 1943) Underhill estimated that the oedema volume in a burn involving one sixth of the body area of rabbits was 70 per cent of the plasma volume

The severity of burning is important (Leach Peters and Rossiter 1943 Sevitt 1957) As is shown in Fig 19 burning at 60° C for 5 seconds produced little or no increase in the water content of guinea pig skin oedema developed in 10-second burns and was maximal in the 30-second and 60-second burns. In the last mentioned, after 1 hour the water content of the skin and subcutaneous tissue was nearly three times normal by 4 hours oedema was maximal and the water content was three to four times normal If such a burn involved one sixth of the body area the oedema volume would amount to 70–100 per cent of the animal s plasma volume Even 30 hours after burning gross oedema was present but it is probable that most of

this fluid had left the circulation much earlier and had not yet been reabsorbed

Delayed increase in oedema—In some burns the oedema substantially increases several hours after burning following an earlier moderate increase For example, in the burn at 60° for 10 seconds

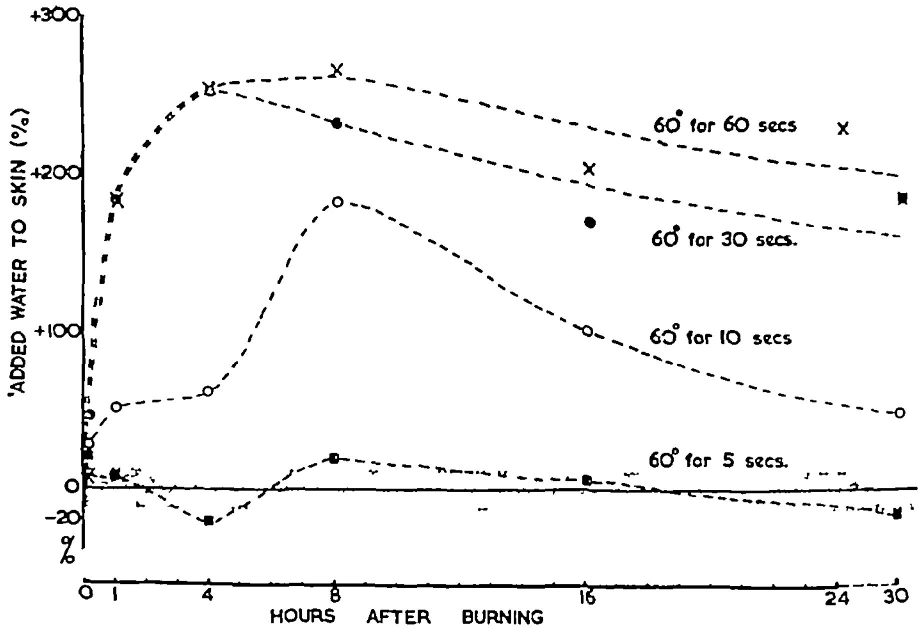


FIG 19—Rate of formation, degree and duration of oedema in guinea-pig skin burned at 60°C for 5, 10, 30 and 60 seconds given as percentage of the mean water content of normal skin In the burns for 60 and 30 seconds there is a rapid and considerable increase in the water content of the skin and subcutaneous tissue, and at 1 hour the added water is nearly twice the water content of normal skin, oedema is maximal by 4–8 hours and gross oedema persists for more than 30 hours In the burns for 10 seconds the degree of oedema is moderate during the first 4 hours, a *delayed* increase is apparent at 8 hours and thereafter oedema decreases No significant oedema occurred in the 5-second burns The shaded area represents the standard deviation of the water content of normal skin Each point is the mean of 12–18 observations obtained by wet-dry weight estimation of excised portions of the skin

(Fig 19) the water content of the skin was 50–60 per cent above normal between 1 and 4 hours after burning, but during the next 4 hours the oedema increased to 180 per cent Injection of Evans blue into the animal's blood-stream showed that the increasing oedema at this time was associated with a delayed increase of permeability in the subcutaneous capillaries

Blood flow and burn oedema—Burning causes an immediate and considerable increase in the flow of blood through the main vessels of

the part presumably reflexly induced This falls after the act of burning and returns to normal during the next few hours (Courtice 1946 Langohr and his colleagues, 1949) Courtice found that when the flow of blood in the scalded leg of a rabbit was decreased by ligating the femoral artery the subsequent oedema of the leg was considerably reduced Furthermore when the scalded paw of a dog was immersed in ice water there was a parallel reduction in the burn oedema lymph flow and blood flow through the leg When the scalded limb was subsequently maintained at 37°C there was a parallel increase in oedema lymph flow and blood flow through the part.

Analysis of the exudate—The crystalloid and electrolyte content (glucose sodium, chloride urea) of blister fluid, oedema fluid and of lymph flowing in the efferent trunk from the burned area are much the same as their concentration in the plasma.

Protein—Unlike normal tissue fluid or lymph the protein content of blister fluid oedema fluid and lymph is generally high Subcutaneous oedema fluid removed from animals within 24 hours of burning has about 80 per cent of the protein content of the plasma (Underhill Kapsinow and Fisk 1930 Beard and Blalock 1931 Bellis, 1942) Blister fluid in man removed during the first 2 or 3 days usually contains about 5 grammes per cent of protein (Mörner 1895 Pack 1926 McIver 1933) Afterwards the protein content decreases but it is not known whether this is due to diminished permeability to local katabolism or to reabsorption The highest protein content is always a little lower than that of the plasma.

The increase in oedema with severity of burning has already been discussed and there is evidence that the severity of burning is not only reflected in the volume of fluid leaving the capillaries but also in its protein concentration This is difficult to demonstrate in vesicle fluid because blisters generally form only when the rate of exudation and the protein concentration are high but it may account for the variations of 3–6 grammes per 100 millilitres which can be found in recently formed fluid Considerable differences in protein concentration related to severity of burning have been demonstrated experimentally in the lymph draining from burns (Cope and his colleagues 1949) In threshold burns the slightly increased flow of lymph has a protein concentration of normal lymph (1–2 grammes per 100 millilitres) with increase of burning severity the protein concentration rises and in severe burns the maximal concentration is about 5 grammes per 100 millilitres (Fig 22) This suggests that in supra threshold burns the oedema is a mixture of fluids of different protein concentrations exuding from capillaries with different

this fluid had left the circulation much earlier and had not yet been reabsorbed

Delayed increase in oedema—In some burns the oedema substantially increases several hours after burning following an earlier moderate increase For example, in the burn at 60° for 10 seconds

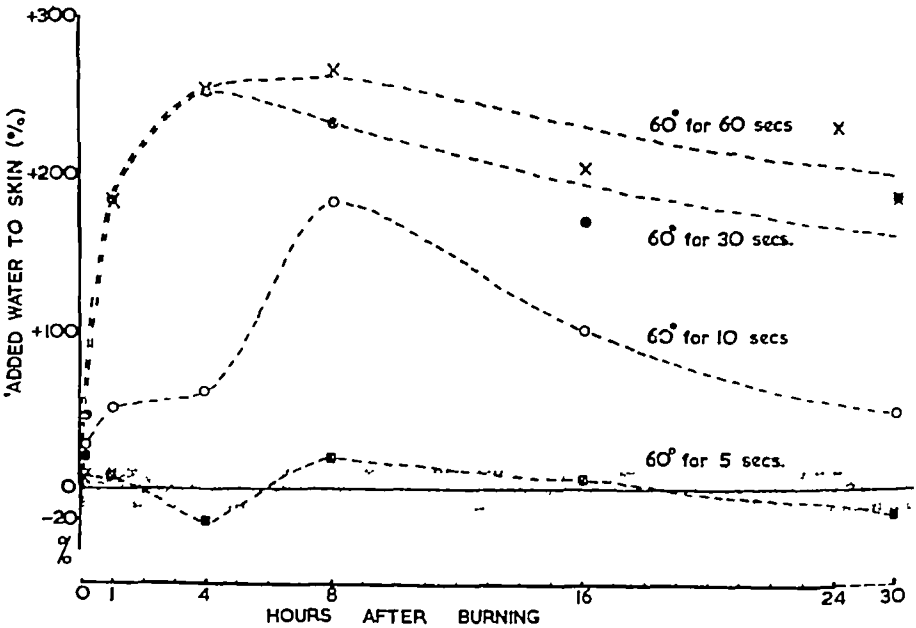


FIG 19—Rate of formation, degree and duration of oedema in guinea-pig skin burned at 60°C for 5, 10, 30 and 60 seconds given as percentage of the mean water content of normal skin In the burns for 60 and 30 seconds there is a rapid and considerable increase in the water content of the skin and subcutaneous tissue, and at 1 hour the added water is nearly twice the water content of normal skin, oedema is maximal by 4–8 hours and gross oedema persists for more than 30 hours In the burns for 10 seconds the degree of oedema is moderate during the first 4 hours, a *delayed* increase is apparent at 8 hours and thereafter oedema decreases No significant oedema occurred in the 5-second burns The shaded area represents the standard deviation of the water content of normal skin Each point is the mean of 12–18 observations obtained by wet-dry weight estimation of excised portions of the skin

(Fig 19) the water content of the skin was 50–60 per cent above normal between 1 and 4 hours after burning, but during the next 4 hours the oedema increased to 180 per cent Injection of Evans blue into the animal's blood-stream showed that the increasing oedema at this time was associated with a delayed increase of permeability in the subcutaneous capillaries

Blood flow and burn oedema—Burning causes an immediate and considerable increase in the flow of blood through the main vessels of

of therapy Indeed blister fluid as one would expect is stagnant and not static

LYMPHATICS AND LYMPH FLOW

Lymphatic permeability—Within a minute or two of burning, the lymphatic capillaries become excessively permeable and readily allow large molecular compounds like haemoglobin or pontamine sky blue to escape into the burned area (McMaster and Hudack 1932) Soon after injecting the dye into the lymphatics draining to the burn, dye stained lymph is rapidly exuded when it reaches the burned area and mixes with the exudate from the blood capillaries (Fig 20) However the contribution of lymph to the exudate is probably not quantitatively important

Increased lymph flow—Starling (1894) was the first to demonstrate that the efferent flow of lymph from the foot of a dog considerably increases after burning and that the lymph has a high protein content The first increase in the efferent lymph flow (in dogs) occurs when the temperature of the immersing water is raised to between 50° and 60°C (Field Drinker and White 1932) but various minimal combinations of temperature and duration of burning also just produce this effect (Cope and his colleagues, 1949) The variations in protein concentrations with severity of burning have already been mentioned

The rapid and considerable increase in the flow of lymph which occurs after severe burning reaches its maximum rate an hour or so later (Fig 22) but within a few hours the flow lessens considerably although it remains above normal

The rapid increase of flow is related to the rapid exudation from the blood capillaries into the interstitial tissues and thence through the permeable lymphatic capillaries. These become passively dilated because their walls are attached to the connective tissue in the dermis which becomes distended by oedema (Pullinger and Florey 1935)

Lymph stasis.—McMaster and Hudack (1934) found that after a rather severe burn of a mouse s ear the lymphatic capillaries in the central area remained patent for 2 hours but by 4–6 hours after burning the capillary lymph flow within the central burn oedema ceased although lymph flowed freely in the peripheral area of graded damage When a solution of a large molecular dye was injected into the skin it now failed to enter the lymphatics of the central area but passed easily into the surrounding lymph capillaries and into the efferent lymphatic trunk (Fig 21) This remained patent for at least 2 days This *stasis* of the central lymph flow is somewhat

degrees of permeability Those near the skin surface receive the greatest damage and there is a vertical gradient of capillary damage through the dermis The protein content of the fluid oozing from the superficial capillaries should be higher than that oozing from the deep capillaries and the protein content of the whole exudate should reflect these differences In most exudates the protein content is probably near-maximum because the volume of fluid contributed by severely damaged capillaries is much greater than that from those only slightly affected

Differential analysis by fractionation or paper electrophoresis shows that there is sometimes a relative increase of albumen over globulin in the early exudate The selective exudation of albumen probably results from its smaller molecular size Often, however, the various protein fractions in the exudate are in about the same proportions as in normal plasma

In extensively burned patients the blister fluid may be tinged red by diffusion of haemoglobin resulting from intravascular haemolysis

Clotting factors.—Some blister fluids contain fibrinogen and prothrombin, and like plasma will not clot before removal Titration of the antithrombin and fibrinolytic activity after clotting *in vitro* gives results similar to those found in blood serum (Macfarlane, 1943) Fluid from other blisters is aspirated with difficulty because having wholly or partly clotted it is bound up in a soft fibrinous gel Its fibrinogen and prothrombin content will be reduced or absent

Lipids.—Significant changes in the lipids of the lymph draining from a burned area were reported by Payne and Krauel (1954) Although the total lipid concentration was unaltered there was a definite rise in the cholesterol, lipid-phosphorus and possibly glycerol concentration associated with the increased lymph flow (*see* page 39) The significance of these findings is unknown but Payne and Krauel raised the possibility that the absorption of lipid breakdown products by red cells may be related to acute haemolysis

Abnormal constituents.—*See* Chapter 12

Stagnation of blister fluid.—Blister fluid is not a *static* pool because diffusible compounds like sulphonamides and antibiotics pass into it from the blood-stream this may occur even days after burning The diffusion however is not as prompt and as free as Cope and his colleagues (1948) suggested because, according to their own results, orally administered sulphadiazine appeared in the plasma hours earlier than in the blister fluid and the plasma concentration of the drug was always greater than the blister fluid concentration during the course

comparable to the blood capillary stasis which develops after severe burning *Its occurrence explains the later decline in the increased* rate of the lymph flow from a severely burned area This reduction

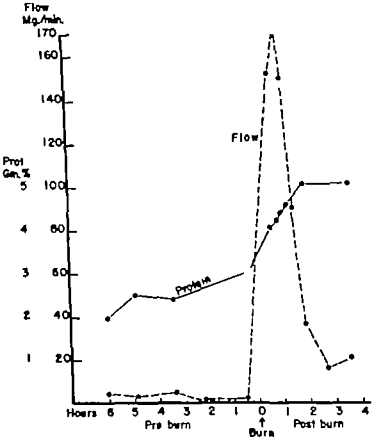


FIG 22.—Increase of lymph flow and lymph protein concentration from a burned area Lymph was collected by cannulating the lymphatic trunk of a dog above the ankle joint. After immersing the paw in water at 100°C for 20 seconds there was a rapid increase in the flow of lymph the protein concentration of which rose to 5 grammes per 100 millimeters. Two to four hours after burning, the lymph flow had fallen considerably but was still above normal. The reduced flow suggests that capillary lymphatic stasis had occurred through much of the burned skin. (*By courtesy of Dr O Cope and the Editors of Arch. Surg* See *Cope and his colleagues* 1949)

in flow has been attributed to a delayed thrombosis of the lymph in the burn (Glenn Petersen and Drinker 1942) but if thrombosis occurs it must be restricted to only a part of the burned area because the lymph flow from the main efferent trunk continues at a relatively high rate—otherwise the efferent trunk would become blocked by

FIG 20—Increase of permeability of lymphatic capillaries after burning The mouse's right ear was warmed at 43°C for 5 minutes Ten minutes later pontamine dye solution was injected into the skin at the periphery of both ears and was taken up by the lymphatics The photograph taken 10 minutes later shows escape of dye all along the lymphatic channels of the heated right ear whilst none was escaping in the left (control) ear (× 3½) (*By courtesy of Dr P D McMaster, Dr S S Hudack and the Editors of J exp Med*)

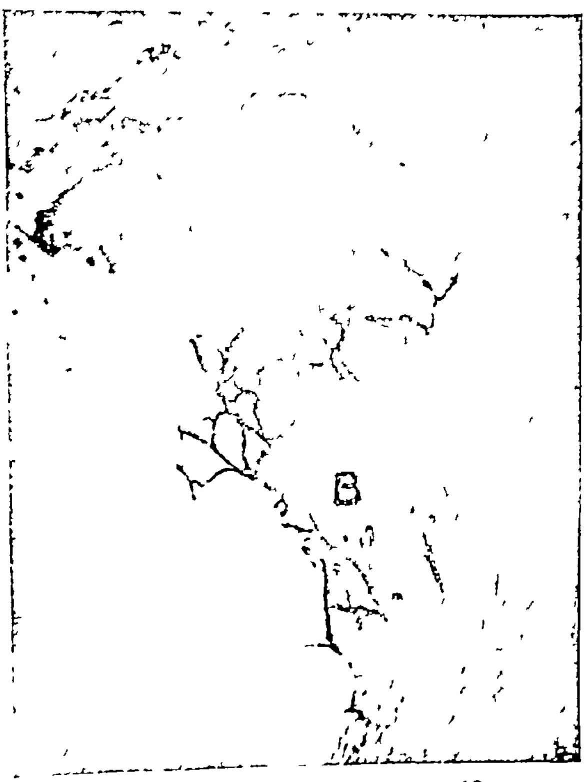


FIG 21—Lymph stasis after burning Three hours previously a small "third-degree" burn was made between the tip and the base of the mouse's ear, and 3 minutes before the photograph was taken pontamine dye solution was injected intradermally at the ear margin (large black blob in top half of figure) Dye escaped from the lymphatics *around* the burn but the burned area (B) was almost unstained Note that the efferent lymph capillaries are patent (× 6) (*By courtesy of Dr P D McMaster, Dr S S Hudack and the Editors of J exp Med*)

comparable to the blood capillary stasis which develops after severe burning. Its occurrence explains the later decline in the increased rate of the lymph flow from a severely burned area This reduction

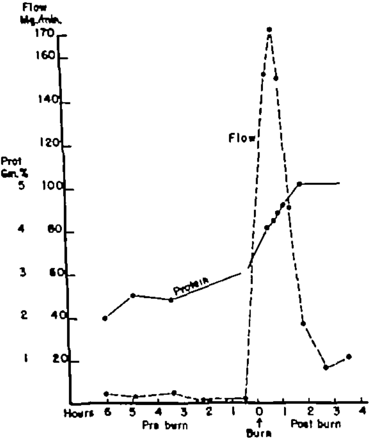


FIG 22.—Increase of lymph flow and lymph protein concentration from a burned area Lymph was collected by cannulating the lymphatic trunk of a dog above the ankle joint. After immersing the paw in water at 100°C for 20 seconds there was a rapid increase in the flow of lymph the protein concentration of which rose to 5 grammes per 100 millimeters. Two to four hours after burning, the lymph flow had fallen considerably but was still above normal The reduced flow suggests that capillary lymphatic stasis had occurred through much of the burned skin. (*By courtesy of Dr O Cope and the Editors of Arch Surg* See *Cope and his colleagues* 1949)

in flow has been attributed to a delayed thrombosis of the lymph in the burn (Glenn Petersen and Drinker 1942) but if thrombosis occurs it must be restricted to only a part of the burned area because the lymph flow from the main efferent trunk continues at a relatively high rate—otherwise the efferent trunk would become blocked by

thrombosed lymph and lymph flow would cease Glenn and his colleagues also claim that the burn oedema is reduced by heparinization of the animal This suggests that lymph clotting plays a part, perhaps a secondary role, in lymph stasis

The continued lymph flow at a lower than maximal rate must be the result of continued lymph drainage from the less severely burned area around and deep to the central zone of capillary lymph stasis as was shown by McMaster and Hudack (1934) In the peripheral zone capillary exudation continues and neither lymphatic nor blood capillary stasis develops

PATHOGENESIS OF THE INFLAMMATION OF BURNS

Histamine—Unna (1896) suggested that "the inflammation was chemically induced and the chemotaxis of the products resulting from the burn measured its degree" This theory was extended by Ebbecke (1923) to damaged tissue of all kinds, and Lewis (1927) asserted that the compound liberated from the skin which produced capillary dilatation and increase of permeability was histamine or a histamine-like substance He suggested that oedema, blistering and peripheral extension of the erythema beyond the burn site was due to the release of larger amounts of histamine which acted both directly on the vessels and by stimulating local axon reflexes

There is no reasonable doubt that histamine is liberated after burning *In vitro* heating of skin subsequently placed in saline is followed by the release and diffusion of histamine and the amount liberated depends on the time and temperature of heating (Rosenthal and Minard, 1939, Rosenthal, Samet, Winzler and Shkolnik, 1957) In these experiments histamine did not diffuse into the immersing medium after heating at temperatures under 55°C whilst the greatest concentration was found after heating at 65°–75°C for 20 minutes Gromakovskaia and Kaplan (1943) examined the blood and cerebrospinal fluid of dogs subjected to trauma and burning and found that they developed histamine-like properties for the isolated stomach, heart and mesenteric blood vessels The formation and liberation of histamine was confirmed by Dekanski (1945) and by Kellaway (1947) Nevertheless liberation of histamine does not necessarily mean that it is responsible for the permeability and other inflammatory changes produced in burned skin—nor for any of the effects of burn shock Indeed antihistamine drugs failed to alter the inflammatory effects in controlled experimental burns on animals and on human volunteers (Sevitt, 1949*b*, Weeks and Gunnar, 1949, Sevitt and his colleagues, 1952) Thus the part played by the release

of histamine in the response of skin vessels to heat cannot be important

Leukotaxine and skin proteinase —Menkin (1936 1940) demonstrated that cell free inflammatory exudates from various sources contained a substance which had the property of increasing capillary permeability and of attracting leucocytes This substance to which he gave the name leukotaxine is a mixture of polypeptides of comparatively low molecular weight (Duthie and Chain 1939 Spector 1951) It or they can be produced *in vitro* by digesting fibrin or serum albumen with pepsin

The mechanism by which leukotaxine appeared in inflammatory exudates remained open to speculation until a clue was provided by Beloff and Peters (1945) who isolated a proteinase from normal skin This is a relatively heat stable proteolytic enzyme active at neutral pH After burning a decrease in the proteinase activity of the skin occurred and this was apparently the result of release of the enzyme and not due to inactivation or other causes (Beloff and Peters 1946) They suggested that skin proteinase might explain the appearance of Menkin s leukotaxine Cullumbine and his colleagues showed firstly that enzymic hydrolysis of fibrin and albumen by skin proteinase produced leukotaxine secondly that a considerable amount of leukotaxine could be extracted from the burned skin of rabbits, and thirdly that leukotaxine was present in the vesicle fluid of heat and mustard burns (Cullumbine and Rydon 1946 Cullumbine McDonald and Simpson 1947) They also found that subcutaneous injection of leukotaxine in a quantity similar to that extractable from burned skin produced a marked local oedema and haemoconcentration in rabbits like that found in burned animals Their evidence that leukotaxine is liberated after burning and is itself formed by the heat liberation of skin proteinase could mean that leukotaxine is responsible for the increased capillary permeability and oedema in burns The leukotaxine theory however fundamentally resembles that of Lewis s histamine theory and is subject to similar criticism Before it can be accepted it will be necessary to produce a substance antagonistic to leukotaxine and subject the theory to a critical trial

Nevertheless the occurrence of a *delayed* permeability change and a *delayed* increase in oedema after certain burns (Sevitt 1954 1957) could be explained by the formation and diffusion of a chemical substance like leukotaxine acting on capillaries unaffected directly by the heat Furthermore leukotaxine diffusion could also help to explain why many leucocytes appear in the deeper part of the dermis and in the skin immediately around a burn

Heat.—The very rapidity with which the vessels of the skin respond to heat indicated to Cohnheim (1873) that it was the rise in temperature itself which produced the changes He suggested that a direct heat-induced "molecular change" affected the capillary endothelium The author agrees with Cohnheim that the early changes in the blood vessels of burned skin are the result of a direct heat effect because it seems unlikely that a chemical compound like leukotaxine could be released and act so rapidly

Nervous activity.—The inflammatory changes are not the result of nervous stimulation since all the phenomena of heat inflammation occur in denervated skin This does not mean that the nervous system does not modify the inflammatory reaction For example, the capillary permeability threshold is increased when the skin is denervated (Sevitt, 1954)

One side of the trunk of guinea-pigs was denervated by unilateral section of the spinal nerves a few weeks later Evans blue was introduced into the blood-stream and burns of the same temperature for the same periods of time were inflicted on anatomically similar sites on the intact and on the denervated sides of the animal Burns which just produced a definite increase of capillary permeability in the intact skin failed to affect the capillaries of the denervated skin (Fig 23) The lowest or threshold temperature which increased the capillary permeability was 2°–3°C higher for denervated skin than for intact skin This is consistent with the observation that transection of the spinal cord decreased the inflammatory oedema and degree of haemoconcentration after burning (Kabat and Hedin, 1942) Development of this work would be of great interest not only for burns but for the whole problem of acute inflammation

MEANS AND AGENTS POSSIBLY INFLUENCING HEAT INFLAMMATION

If the inflammatory reaction in burned skin could be modified to reduce the leakage of fluid from the capillaries the threat and dangers of plasma oligaemia might be reduced or avoided The means and agents worthy of consideration at present are (1) increasing the tissue pressure by restrictive bandages, (2) local cold therapy and (3) various drugs—particularly antihistaminic compounds, cortisone, ACTH, adrenocortical extracts and "endothelial-sealing agents"

Tissue pressure and restrictive bandages—The colloid osmotic pressure difference between capillary blood and burn exudate is virtually zero because of the high protein content of the latter As a consequence the effective filtration pressure becomes the difference between the capillary hydrostatic pressure and the tension in the

tissues At first the latter is low only 1–3 mm Hg but as oedema distends the tissue spaces the tension rises The rise of tension is influenced by the distensibility of the tissue and more fluid would have to accumulate in a loose than in a tight tissue to produce the same increase The tissue tension following experimental burns at 60°C for 30 seconds in the rabbit increased to between 12 and 31 mm Hg (mean 21 mm.) the difference between the capillary hydrostatic and tissue pressure was reduced but the former was always 1–17 mm Hg *greater than the latter* and *therefore* fluid continued to leak (Bellis, 1942)

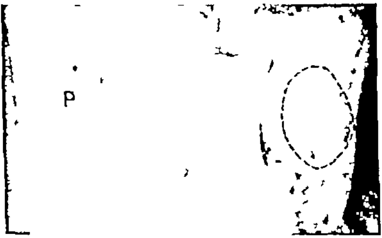


FIG 23 —Experimental burning of denervated skin. Right-sided abdominal anaesthesia and palsy were produced in guinea-pigs by unilateral section of the thoracolumbar spinal nerves. Two months later similar burns were made on the right (anaesthetic) and left sides of the animal after intracardiac injection of Evans blue. In the photograph showing part of a guinea-pig's back the results of two minor burns are recorded. The anaesthetic skin is outlined in pencil. The burn on the left side produced a circular blue patch of skin (P) corresponding to the site of application of the burning iron and indicating increased permeability of the dermal capillaries. However dye did not appear in the homologous burn on the right side, the site of which is outlined by dots

If the tissue tension could be raised above the capillary pressure exudation should cease This can be done by applying external pressure to the burned area In experimental animals it has been shown that when a plaster cast was firmly applied or the pressure raised by other external means the oedema of the burned part was greatly reduced and so were the efferent lymph flow the total fluid lost from the circulation and the degree of haemoconcentration (Barnes and Trueta 1941 Glenn Gilbert and Drinker 1943 Rossiter 1944 Cameron and his colleagues 1945) For example

Rossiter found that an external pressure of only 10 mm Hg (applied by an air cuff) greatly reduced the oedema in burned guinea-pig and rabbit skin The pressure is most effective if applied immediately after burning because oedema forms rapidly

In clinical practice the application of a skin-tight plaster would be of value only when it was applied skilfully and very soon after burning Danger could arise in inexpert hands if the arterial blood flow were interrupted The pressure dressing technique is only practical for burns on the limbs and has been widely practised, particularly in the United States of America (Allen and Koch, 1942, Siler and Reid, 1942) Whatever the merits of the technique, and these are limited, its application should not cause delay in the transfusion of the extensively burned patient

Local cold therapy.—Cold water was known to the ancients as a useful measure in the treatment of burns probably because of the relief of pain Hastings (1820) found that when the web of a frog's foot was burned the blood flow quickened, but if he applied ice to the burn the vessels contracted and the local circulation was reduced

The rate of formation of oedema in a burned part is not only dependent on the difference between the capillary hydrostatic pressure and tissue pressure (colloid osmotic pressure difference having been abolished) but also on the rate and volume of the blood flow through the affected capillaries If these can be reduced by therapy the rate of exudation will decrease

Experimentally it has been found that immersion of a burned limb in cold water considerably reduces the local oedema (Courtice, 1946, Langohr and his colleagues, 1949) For example, Courtice showed that when two legs of a rabbit were scalded, one being subsequently immersed in water at 37°C and the other in ice-water, the oedema was about three times as great in the former as in the latter The lymph flow from the burn and the blood flow through the scalded limb were similarly affected He also found that the longer the limb was maintained in ice-water up to 48 hours the less the subsequent oedema and haemoconcentration when the part was warmed Similarly Langohr and his colleagues found that after burning, the flow and protein concentration of lymph were reduced and oedema retarded during exposure to cold (10 C) They believed that the effect of cold was due to shunting of blood away from the damaged capillaries

It is tempting to recommend cold therapy for burns but caution must be exercised It is not known whether cold will have the same effect on burned human skin as on the skin of animals Moreover,

prolonged immersion of a large area of the body in cold water would reduce the general body temperature and prolonged or severe cooling might be injurious to already damaged skin Cold water immersion therapy was used by Rose (1936) in treating burns and he was favour ably impressed by the results

DRUGS

Various local and systemic drugs have been used in the treatment of burns in the belief that they reduce the oedema Here antihist amine drugs cortisone and adrenocortical extracts (none of which have any beneficial effect) will be discussed Finally a promising line of research will be briefly considered the use of endothelial sealing agents

Antihistamine drugs —Acting on the assumption that histamine plays a part in the inflammation of burns Milne Balfour and Yeoman (1951) administered antazoline to recently burned patients and claimed that it abolished blistering and oedema Other claims for the beneficial effect of various antihistaminics were also made in the correspondence columns of the *British Medical Journal* at the time Sevitt (1949*b*) had previously found that the protection of guinea pigs against the action of histamine by various powerful antihistamine preparations had no detectable effect on controlled experimental burns of various degrees of severity The changes investigated included erythema, capillary permeability qualitative blood flow changes in the skin the degree of clinical oedema and the subsequent healing of the burns Similarly Weeks and Gunnar (1949) using rabbits showed that an antihistaminic failed to alter the increase of capillary permeability or the histological inflammatory picture Subsequently a controlled burning experiment on human volunteers confirmed that an antihistaminic was without effect on oedema blister fluid cellular exudate vascular changes or healing (Sevitt and his colleagues 1952) and Butterfield (1957) found that promethazine cream failed to influence vesication although it modified the flare in the surrounding skin These experiments indicate that antihistamines have no place in the treatment of burns

Cortisone adrenocortical extracts and ACTH —Adrenocortical ex tracts have been used for burns and shock often in the belief that they reduce the capillary permeability in the damaged area and more recently cortisone and ACTH have been administered to extensively burned patients sometimes for similar reasons (Chapter 18)

Cortisone and ACTH can reduce the inflammatory oedema of the tuberculin test (Long and Miles 1950) and of other allergic reactions presumably by interfering with an antigen antibody reaction, but a

number of workers have claimed that they have a "non-specific antiphlogistic action For example, Selye (1949) claimed that the inflammatory swelling after an injection of formalin was inhibited by cortisone or ACTH If this were so the anti-inflammatory power would be exercised 'non-specifically' and the drugs would be expected to suppress or reduce other forms of acute inflammation including that of burns Selye's results were subsequently criticized on statistical grounds

The effect of adrenal cortical extract (and of pituitrin) on the abnormal permeability of burned skin was studied by Cope and his colleagues (1949) by estimating the flow and protein content of the lymph from the feet of dogs subjected to standard burns They found that neither of these agents had any significant effect Later Raker and his colleagues (1951) found that ACTH had no effect on the capillary permeability in burns on dogs or man

The possible effect of cortisone on the rate of formation and the degree of oedema and on the permeability and blood-flow changes through the skin following standard burns of different degrees of severity was investigated by Sevitt (1954 1957) in rabbits and guinea-pigs No significant differences were found between the animals receiving cortisone and the control animals Butterfield (1957) found that blistering erythema and peripheral flaring of standard experimental burns on human volunteers were not influenced by the prior administration of ACTH or the early use of cortisone cream It may be concluded that ACTH, cortisone and adrenal cortical extracts have no effect on the acute inflammation of burns

Endothelial-sealing agents—When brilliant vital red was injected into the blood-stream of a guinea-pig before or after burns (of a certain severity) had been inflicted the dye diffused into and stained the burned skin a deep red colour (Sevitt 1949*a*) When Evans blue was subsequently injected into the blood it *sometimes* failed to stain the red-dyed burned areas of skin This effect was distinguished from the reaction of stasis because the narrow blue rim of the latter (due to graded vascular damage at the edge) did not develop around the site of application of the burning iron In other words a circulating dye failed to stain burned skin the capillaries of which should have remained excessively permeable at the time of injection This might have been due to one of two causes The red dye may have combined with all the available protein in the plasma leaving none for combination with the subsequently injected Evans blue, but this was unlikely because the blue dye diffused into burns subsequently inflicted on other parts of the animal's body The other possibility was that the

brilliant vital red plasma protein complex had affected the abnormal capillaries in the burn had sealed or blocked the permeable capillary endothelium making it impossible for further exudation to occur

The occasional effect of brilliant vital red is reminiscent of the work of Chambers and Zweifach (1940 1947) and Danielli and Stock (1944) who showed that the oedema of organs was decreased by the presence of colloids in the perfusion fluid and who suggested that this was partly due to an endothelial sealing activity In other words, colloids from the blood plasma might coat the capillary endothelium and reduce its porosity

Recently the effect of intravenously injected polysaccharides of high molecular weight on the permeability of capillary endothelium has been studied by Shilo Wolman and Hestrin (1954) and Davies Shilo and Hestrin (1955) Injection of native levan (prepared from growing *Aerobacter levanicum* in a sucrose medium) was found to suppress or reduce the *inflammatory* response produced by the injection of turpentine or *Staphylococcus aureus* into the skin of animals as measured by the extravasation of intravenously injected trypan blue The effect appeared to depend partly on the high molecular weight of the substance and partly on its highly branched molecular structure Dextran of similar molecular weight was less effective Compounds of this kind offer a hope that the gross oedema of extensive burns might be reduced considerably

Considerable experimental work is necessary because endothelial sealing agents also have a special potential danger in that they may promote local bacterial invasion by reducing the exudation of antibacterial humoral substances from the plasma

REFERENCES

Allen, H S and Koch S L (1942) *Surg Gynec Obstet* 74 914

Barnes, J M and Trueta J (1941) *Lancet* 1 623

Beard, J W and Blalock A (1931) *Arch Surg* 22, 617

Bellis, C J (1942) *Surgery* 12, 251

Beloff A., and Peters, R. A (1945) *J Physiol* 103, 461

— — (1946) *Ibid.*, 105, 54

Blalock, A. (1931) *Arch Surg* 22, 610

Butterfield W J H (1957) *Surg Gynec Obstet* 104, 53

Cameron, G R. Allen, J W Coles, R. F G and Rutland J P (1945) *J Path Bact* 57 37

Chambers R and Zweifach, B W (1940) *J cell comp Physiol* 15, 255

— — (1947) *Physiol Rev* 27 436

Cohnheim, J (1873) *Neue Untersuchungen uber die Entzundung* Berlin Hirschwald

Cope O Graham, J B Moore F D and Ball M R (1948) *Ann Surg* 128, 1041

— — Graham, J B Mixter G and Ball M R (1949) *Arch Surg* 59 1015

Cope, O , and Moore, F D (1944) *J Clin Invest*, **23**, 241
Courtice, F C (1946) *J Physiol*, **104**, 321
Cullumbine, H , and Rydon H N (1946) *Brit J exp Path*, **28**, 33
— McDonald, I and Simpson M M (1947) *J Path Bact*, **59**, 467
Danielli, J F , and Stock, A (1944) *Biol Rev* **19**, 81
Davies, A M , Shilo, M and Hestrin, S (1955) *Brit J exp Path*, **36**, 500
Dekanski J (1945) *J Physiol*, **104**, 151
Duthie, E and Chain E (1939) *Brit J exp Path*, **20**, 417
Ebbecke, U (1923) *Pflug Arch ges Physiol*, **199**, 197
Field, M E , Drinker, C K and White, J C (1932) *J exp Med*, **56**, 363
Glenn, W W L , Gilbert, H H and Drinker, C K (1943) *J clin Invest*, **22**, 601
— Petersen D K , and Drinker, C K (1942) *Surgery*, **12**, 685
Gromakovskaia, M M , and Kaplan, L E (1943) *Bull eksp biol med*, **15**, 12
Ham, A W (1944) *Ann Surg*, **120**, 689
Harkins H N (1934) *Proc Soc exp Biol, N Y*, **31**, 994
— (1935) *Arch Surg*, **31**, 71
Hastings, C (1820) *A Treatise on Inflammation of the Mucous Membrane of the Lungs To which is Prefixed an Experimental Enquiry Respecting the Contractile Power of the Blood Vessels and the Nature of Inflammation* London
Kabat, H , and Hedin, R F (1942) *Proc Soc exp Biol Med*, **49**, 114
Kellaway, C H (1947) *Edin med J*, **54**, 333
Kreyberg, L (1949) *Physiol Rev*, **29**, 156
— and Vermes, E (1946) *Acta Path microbiol Scand*, **23**, 265
Landis, E M (1936) *Harvey Lectures*, 70
— (1937) *Amer J med Sci*, **193**, 297
— and Gibbon, J H (1933) *J clin Invest*, **12**, 105
Langohr, J L , Rosenfeld, L , Owen, C R , and Cope, O (1949) *Arch Surg*, **59**, 17
Leach, E H , Peters, R A , and Rossiter, R J (1943) *Quart J exp Physiol*, **32**, 67
Lewis, T (1927) *The Blood Vessels of the Human Skin and Their Responses* London, Shaw
Long, D A , and Miles, A A (1950) *Lancet*, **1**, 492
Macfarlane, R G (1943) *Brit med J*, **2**, 541
McIver, M A (1933) *Ann Surg*, **97**, 670
McMaster, P D , and Hudack, S S (1932) *J exp Med*, **55**, 431 **56**, 239
— — (1934) *Ibid*, **60**, 479
Menkin, V (1936) *J exp Med*, **64**, 488
— (1940) *Dynamics of Inflammation* New York, Macmillan
Milne, A E , Balfour, K C , and Yeoman, J P (1951) *Brit med J*, **2**, 117
Moritz, A R , and Henriques, F C (1947) *Amer J Path*, **23**, 695
Morner, K (1895) *Skand Arch Physiol*, **5**, 272
Pack, G T (1926) *Arch Path (Lab Med)*, **1**, 767
Payne, J T , and Krauel, K (1954) *Surg Forum*, **5**, 750
Pullinger, B D , and Florey, H W (1935) *Brit J exp Path*, **16**, 49
Raker, J W , Wight, A , Michel, A J D , and Cope, O (1951) *Ann Surg*, **134**, 614
Rose, H W (1936) *Northwest med*, **35**, 267
Rosenthal, S R , and Minard, D (1939) *J exp Med*, **95**, 209
— Samet, C , Winzler, R J , and Shkolnik, S (1957) *J Clin Invest*, **36**, 38
Rossiter, R J (1944) *Lancet*, **1**, 9
Selye, H (1949) *Brit med J*, **2**, 1129
Sevitt, S (1949a) *J Path Bact*, **61**, 427
— (1949b) *Brit J exp Path*, **30**, 540
— (1954) *Proc R Soc Med*, **47**, 225
— (1957) In the press
— Bull, J P , Cruickshank, C N D , Jackson, D McG , and Lowbury, E J L (1952) *Brit med J*, **2**, 57

Shilo M Wolman, B and Hestrin, S (1954) *J biol Chem* 178, 839
Siler V E and Reid M R (1942) *Ann Surg* 115 1106
Spector W G (1951) *J Path Bact* 63 93
Starling, E. H (1894) *J Physiol* 16, 224
Underhill, F P., Kapsinow R and Fisk M E (1930) *Amer J Physiol* 95 302
315 325 330 334 339 348 364
Unna, P G (1896) *Histopathology of the Diseases of the Skin* Edinburgh
Weeks, R. E and Gunnar R. M (1949) *Arch. Path* 48, 178

CHAPTER 4

THE CLASSIFICATION AND HEALING OF BURNS

THE classification and the modes of healing of burned skin must be considered together because the modern classification of the depth of burns is intimately related to their subsequent clinical course

CLASSIFICATION OF BURNS

The oldest classifications of burns naturally correlated the surface appearances with severity of burning, and erythema, vesication, crusting and charring were the basis of the division Later certain outward appearances became associated either with the pathological concepts of inflammation and necrosis or with depth of injury Wiseman (1676) classified gunpowder burns into (1) "Superficial, it raiseth the cuticle up in blisters", (2) "Deeper into the skin it causeth an eschar", and (3) "Deeper into the flesh it makes a hard crust with a contraction" The best known of the older classifications was that of Dupuytren (1832) who divided burns into six numerical degrees of severity largely according to depth but partly according to outward appearance Nevertheless, in 1896 Unna criticized surgeons for regarding " burns from their three most striking results, first redness of the skin, second formation of bullae and third formation of scabs It is thus tacitly assumed that only eschar formation is accompanied by necrosis of the skin, and the fact that every form of burning induces necrosis is consequently overlooked " In the course of time and experience certain outward appearances became associated not only with depth of injury but also with a clinical course A simple erythema indicated rapid healing, and charring the absence of healing, but between these extremes other surface appearances became identified, sometimes correctly, sometimes wrongly, with a subsequent epithelialized or granulating surface

It is now known that the surface appearances of many accidental burns bear little relationship to their clinical course and as a result classifications based on appearance have been abandoned That now adopted is related to the depth of necrosis of skin epithelium (Converse and Robb-Smith, 1944, Gibson and Brown, 1945, Jackson, 1953)

Superficial skin-loss —Necrosis is confined to the epidermis and healing occurs readily with simple desquamation

Partial skin-loss (*p.s.l.* *partial thickness skin loss*) —Destruction of the epidermis and the upper part of the dermis has occurred but sufficient epithelial elements remain in the dermis to allow epithelial resurfacing

Whole skin-loss (*w.s.l.* *full thickness skin loss*) —Complete or virtually complete destruction of all dermal epithelium has occurred Resurfacing by epidermis if at all possible can only take place by epithelialization from the normal epidermis at the edge

DIAGNOSIS OF THE DEPTH OF BURNING

In surgical practice the diagnosis of the depth of necrosis is important because the modern treatment of whole skin loss burns is immediate excision and skin grafting Superficial burning and deep coagulation necrosis are readily recognized but many partial skin loss and whole skin loss burns look alike Neither erythema nor blistering are diagnostic of partial skin loss burns but only indicate an acute inflammatory reaction involving the dermal capillaries At first the erythema may blanche on pressure indicating a dermal circulation but later capillary stasis may supervene When stasis and necrosis are limited to the upper part of the dermis regeneration from the deeper epithelial elements will occur and the burn is a partial skin loss burn but if stasis extends through the whole depth of the skin necrosis will follow—if not already present—and the burn is a whole skin loss burn The depth of capillary stasis cannot be diagnosed by surface examination therefore a non blanching erythema is not a safe clinical criterion for diagnosing the depth of burning Neither is the detection of a dermal circulation during the first hours after burning since stasis may supervene even the following day Furthermore a white necrotic appearance merely indicates that heat necrosis of the upper dermis occurred during early capillary spasm or before erythema developed but it gives no indication as to the depth of necrosis If the white necrosis is superficial the burn may be a partial skin loss burn but if it extends through the dermis it is of whole skin loss depth For this reason the suggestion of Patey and Scarff (1944–45) that a modified Van Gieson s connective tissue stain should be applied to the surface of a burn in order to differentiate heat altered collagen from normal collagen is of no practical value Therefore in many burns surface examination cannot reveal the depth of burning

Sensation in the burned skin.—How then can one distinguish a partial skin loss from a whole skin loss burn ? No ideal solution has been found The best test available is based on the preservation or

destruction of the nerve endings in the skin, particularly pain nerve-endings in the deep part of the dermis The test developed from the observation that hypoalgesia but not analgesia is found in partial skin-loss burns, whilst sensation is lost in whole skin-loss burns (Colebrook Gibson and Todd, 1945, Cope and his colleagues, 1947, Sevitt, 1949, Bull and Lennard-Jones, 1949)

A description of this test as used in the Burns Unit of the Birmingham Accident Hospital has been published by Jackson (1953) The burn is tested for sensitivity to pinprick with a sterile needle About a dozen pricks to the square inch are necessary partly because the pain spots are localized and partly because the whole skin-loss area may be patchy As in all subjective tests the patient must be co-operative and understand what is required of him any pain sensation on pricking indicates partial skin-loss, while whole skin-loss burns are always analgesic However, analgesia may also be found in deep partial skin-loss burns, particularly on the face, scalp, palms and soles This is presumably because some of the sweat coils are situated deep to the deepest level of the pain nerve-endings in the skin and some in the subcutaneous fat In certain chemical burns the test is less reliable (Chapter 24)

THE HEALING OF BURNS

PRINCIPLES

Effective healing of skin means regeneration to normal skin and in particular resurfacing with normal epithelium The power to resurface is inversely dependent on the depth of burning, that is on the depth of destruction of epidermis and of hair follicles and sweat ducts in the dermis In general, superficial and most partial skin-loss burns finally regenerate into normal skin but whole skin-loss burns cannot epithelialize and granulation tissue forms

If the burn is very superficial and part of the epidermis remains viable it rapidly reforms its superficial layers and the skin is virtually restored to normal within a few days (Fig 25)

When the burn destroys the epidermis but leaves the dermis and its epithelial elements intact, resurfacing from the tops of follicles and sweat ducts (according to skin site) restores epidermal cover within a week or 10 days (Fig 26)

If the burn involves the dermis but some dermal epithelium remains viable resurfacing takes place from the tops of the surviving parts of the viable hair follicles and ducts (Figs 27–29) It is complete in 2–6 weeks according to the depth of necrosis within the dermis

When all the epithelium in the skin is destroyed, regeneration from within the burn is impossible and resurfacing can only occur by the spreading of epithelium from the edge (Fig 36) Edge healing also

occurs in burns of lesser depth In small full thickness skin loss burns resurfacing by edge healing is not prolonged but if the burn is large healing is very slow resurfacing is prolonged for months granulation tissue forms and is succeeded by considerable scarring and skin shortage Edge healing is particularly slow in circumferential burns

SURFACE CHANGES IN A TYPICAL ACCIDENTAL BURN

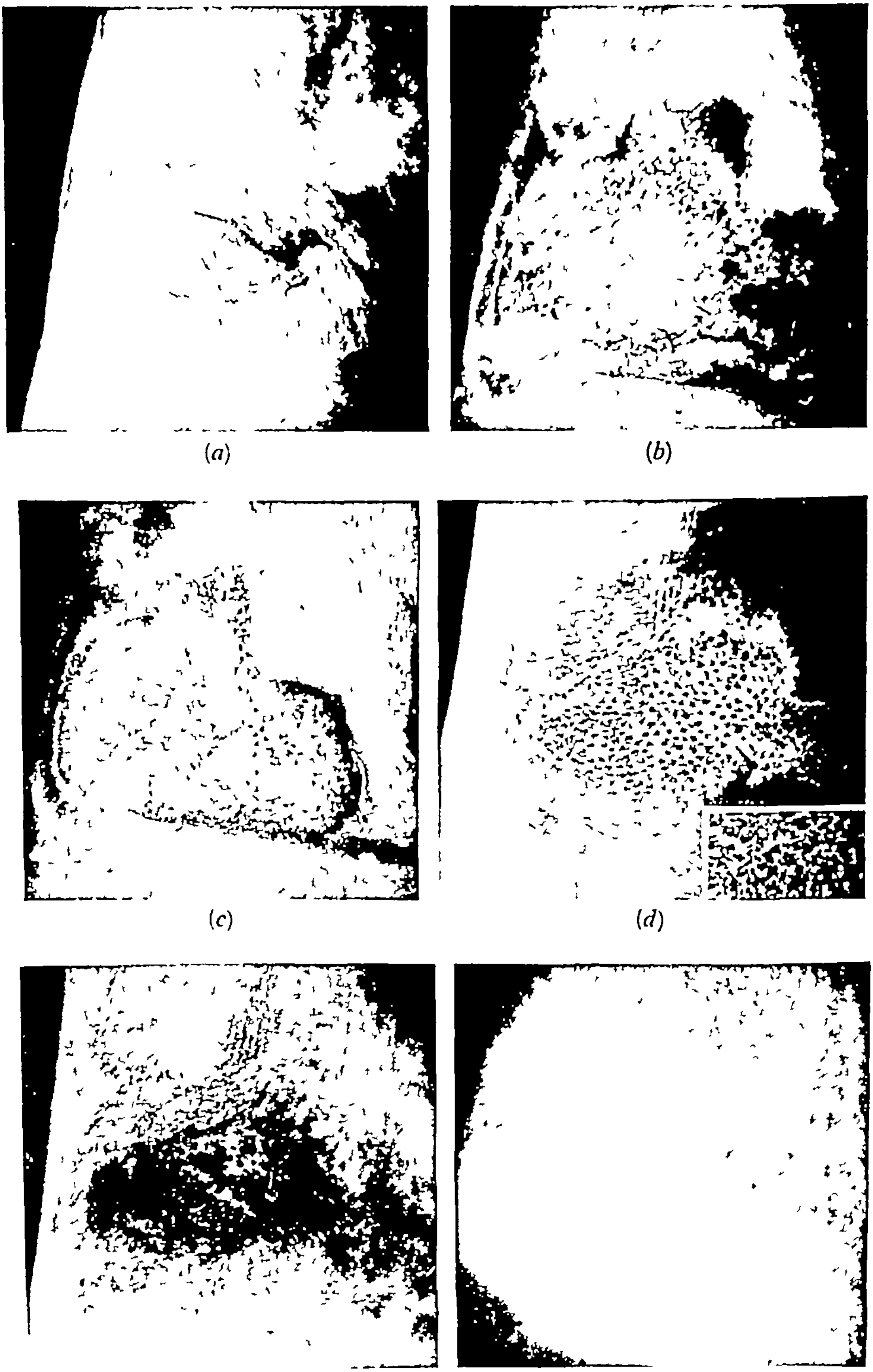
The day to-day changes in appearance depend on the treatment If the burn is exposed and allowed to dry the exudate and necrotic surface skin are transformed into a hard dry crust which conceals the regenerative process deep to it The crust or slough separates naturally when the epithelial surface has re formed but prior to this the deeper skin cannot be inspected without interfering with healing. When the burn is covered with a thick dressing so that it is not allowed to dry the moist fibrinous exudate and the flaking superficial collagen slough are easily removed and the day to-day changes can be inspected A study of these was made by Jackson (1953) in relation ship to the diagnosis of the depth of burning, and the findings were related to the regenerative activity of the skin as revealed histologically

Most accidental burns are most severe in the centre and many have three concentric zones when first examined (Fig 24*b*) these are (1) the outer border of hyperaemia which blanches on pressure and continues to do so after 24 hours (2) an intermediate red zone of capillary stagnation and stasis that is erythema which finally fails to blanche on pressure and (3) a central white ischaemic area due to heat necrosis of at least the superficial dermis. The relative widths of the zones vary considerably from burn to burn and one or other zone may predominate

It is convenient to consider the changes which occur in each area in one burn (Fig. 24)

Changes during the first week —During the first week the appearance depends on the vascular state of the superficial dermis and is largely independent of the subsequent course of the burn The major change is the transformation of the red zone of stasis into a white area resembling the inner zone This is due to degradation of the haemoglobin in the trapped red cells Two zones are now present a hyperaemic border surrounding a central white area (Fig 24*c*)

Changes during the second and third weeks —Epithelialization of the edge is just visible after 5–7 days but is not easy to see at first because the layer is thin and translucent drying and wrinkling the skin allow the edge to be seen readily Histologically epithelial spreading has



(a) (b) (c) (d) (e) (f)

commenced before this and is taking place from the viable edge of the epidermis and from the tops of regenerating hair follicles and sweat ducts in the outer and possibly intermediate zones Progressive inward healing of the edge continues from about the seventh to the fourteenth day It becomes progressively easier to see as the superficial dead dermis is shed and as the new epidermis thickens matures and becomes opaque by keratinization

In the intermediate zone regeneration is rapid when the depth of capillary stasis has been superficial and when many hair follicles survive In such circumstances epithelial spreading continues centrally until about the end of the second week and then appears to cease for a short time

The unhealed area is now smaller and the original burn consists of a central unhealed white zone mottled with red spots and surrounded by a peripherally epithelialized hyperaemic area (Fig 24*d*) The mottling appeared earlier its origin is not certain but in some cases it is due to the exposure of the normal reticular pattern of the deep viable dermis which contains many small red vascular areas within the collagen net It seems that progressive desquamation of the dead surface collagen makes this visible The depth of the desquamating slough determines whether epithelial regeneration from within the white area is possible or whether granulation tissue will form

Epithelialization of the central area—If the slough separates superficially to the sweat coils epithelial resurfacing will occur from the deep parts of the sweat ducts and possibly from a few deeply placed hair follicles The viable surface of the dermis is at last exposed and its surface is seen to be covered with multiple fine red dots (Fig 24*d*) Jackson (1953) drew attention to this appearance which is different

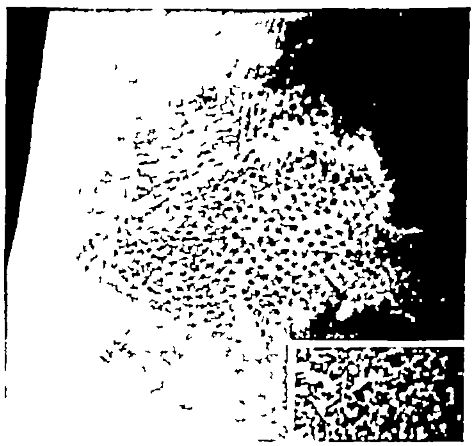
---

FIG 24—Healing of an accidental burn of the thigh. (*a*) Day of burning blistering was present. When the blister top was removed the central area of the burn was white and analgesic and was surrounded by an erythematous zone which blanched on pressure (*b*) Second day three zones are present—peripheral hyperaemia, capillary stasis and central white coagulation. (*c*) Third day only two zones now visible, the peripheral erythema and the remainder which is white but mottled with coarse red dots. (*d*) Thirteenth day epithelialization has spread centrally to a "white line" and multiple fine red dots ("speckling") are just visible except in the deepest central area. Speckling, which denotes sweat-duct healing, is to be distinguished from the coarser red mottling which has become more apparent. The inset shows speckling in another burn at three-quarters natural size (*e*) Twenty-second day the translucent epithelium of the speckled zone has become opaque but the deep central area remained unhealed until the end of the fourth week (*f*) One year normal skin The central two-thirds was pigmented at 3 months but paler than normal at a year (*By courtesy of Dr D MacG Jackson and the Editor of Br J Surg*)

(*a*)

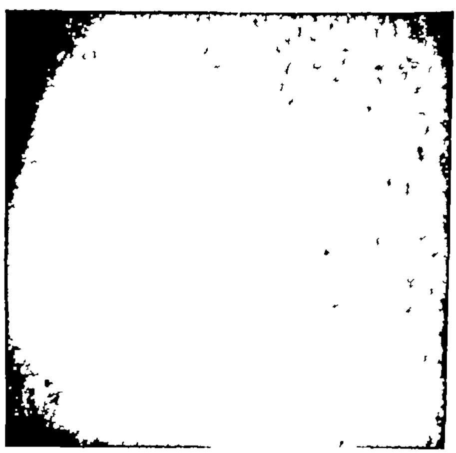
(*b*)

(*c*)



(*d*)

(*e*)



(*f*)

Separation of slough.—In many whole skin loss burns the coagulated slough is deep and perhaps leathery and does not separate by progressive irregular desquamation of the surface as described above but in one piece A line of cleavage between slough and granulation tissue forms about 3 weeks after burning and the whole thickness of the slough can be lifted off the granulating bed

HISTOLOGICAL CHANGES DURING HEALING

Partial skin-loss (p s l) burns are considered first and for descriptive convenience are classified into superficial p s l deeper p s l and deep p s.l burns. Of course all intermediate grades between the superficial and deepest forms occur

Superficial partial skin-loss burns.—When the epidermis is destroyed but there is little or no loss of dermis epithelial resurfacing is rapid The process has been described by Gordon and his colleagues (1946) and resembles the healing of split skin graft donor areas It takes place multifocally from viable epithelial cells lining the upper ends of the follicles and the mouths of the sweat ducts, and also from the edge of the normal skin Within 48 hours of burning, multiple thin islands of migrating epithelium, at first 1 or 2 cells thick are found on the surface (Fig. 26) often under an exudate of fibrin and poly morphs which may contain small bacterial colonies During the next few days a thin continuous epidermal layer closely apposed to the surface is formed due to the coalescence of the spreading islets. Sometimes apposition is partly unsuccessful possibly because of infection and the fibrinous exudate may contain small masses of loose epithelium The process is so active that by 7–14 days the epidermis has become layered and keratinized Stratification is seen first at the mouths of hair follicles and sweat ducts and is accom panied by mitotic evidence of cell division Completion of surface cover is said to be followed by the downgrowth of multiple spurs of epithelium into the upper third of the dermis Gillman and his colleagues (1953–54 1955) described this appearance in the healing of graft-donor areas and suggested that it may occur in healing burns Although there is suggestive evidence in the author s material that a downward invasion of the upper dermis by epithelium may sometimes occur (Fig 32) the appearance may be confused with the hyper plastic process involving sweat ducts and hair follicles which in creases their size and transforms them into apparently solid structures (Figs 30 31 and 32)

The changes affect the sweat ducts and hair follicles in the upper half or so of the dermis The peripheral cells of the follicles become hyperplastic and multilayered and when cut longitudinally off-centre

from the coarser red mottling, and which he called "speckling" He found that the dots were formed of hyperaemic capillaries around sweat ducts The appearance is important to surgeons because it indicates that epithelial healing can take place The surface is already covered by a thin invisible layer of epithelium which during the next week or so thickens and matures Healing in this area is also most rapid peripherally because the centre of the burn is usually the most

FIG 25 —Healing of a very superficial burn at 3 days The necrotic superficial part of the epidermis is flaking off and the deeper viable part is regenerating (Haematoxylin and eosin, × 140)

deeply necrotic part and it may remain unhealed until the end of the fourth week

Granulation tissue formation —If the slough in the central white area separates deep to the sweat coils the inner zone is a whole skin-loss burn and the mottled white area is replaced within 2 or 3 weeks by an oozing vascular granulation tissue

Pigmentation —When resurfacing is complete the skin is often pigmented brown and this gradually disappears during the following weeks or months

they appear as solid columns of rather large angulo-squamous cells (Fig 30) Many nuclei are hyperchromatic and some are in mitosis Similarly the sweat ducts change from a single layer of cubical epithelium to a multiple layered column of metaplastic epidermoid cells (Fig 31) As already noted these epithelial columns may be difficult

FIG 30—Healing of a deep partial skin-loss burn at 14 days the main slough has been removed. A flat island of epithelium is present beneath a very thin slough at the surface. Note (1) the hyperplastic, apparently solid squamous epithelial foci which are transformed hair follicles, (2) the cellular infiltration and oedema of the dermis and (3) the fine elastotically degenerated collagen fibres sloughing at the surface (Haematoxylin and eosin × 75)

FIG 31—Hyperplastic sweat duct in the dermis of a healing partial skin-loss burn of the upper arm. Biopsy 7 days after burning. Note the development of a multi-layered angulo squamous epithelium around the central duct which is lined by cubical epithelium. (Haematoxylin and eosin × 190)

to distinguish from spurs invading the dermis from the new epidermis (Fig 32)

Deeper partial skin-loss burns.—Healing is retarded by disintegrative necrosis of the upper dermis Unlike tissue affected by coagulation necrosis dermis affected by the disintegrative change is broken up and finally liquefied by leucocytic action and is susceptible to bacterial digestion The necrotic area is heavily invaded by leucocytes about 2 or 3 days after burning after which it breaks up and is

FIG 26

FIG 27

FIG 28

FIG 29

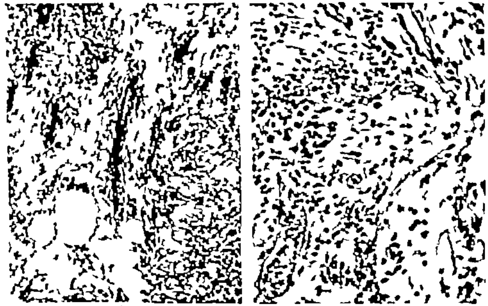
FIG 26—Resurfacing of a superficial partial skin-loss burn at 3 days The old epidermis has disappeared and a flat monolayer of epithelial cells has migrated over the surface of the intact dermis from the mouth of a sweat duct A similar migration occurs at the openings of follicles (Haematoxylin and eosin, × 90)

FIG 27—Resurfacing of a partial skin-loss burn which has been a little delayed Biopsy 8 days after burning Two islands of immature epithelium are present on the new surface of the dermis, part of which has sloughed The new epithelium is surrounded by leucocytes, fibrin and collagen debris and is covered by a scab full of leucocytes, through an artefact this appears separated from the dermal surface (Haematoxylin and eosin × 90)

FIG 28—Resurfacing of a deeper partial skin-loss burn from sweat ducts Most of the slough has separated Note the upward growth of new capillaries, the infiltration of inflammatory cells and the oedema in the dermis Burn of thigh on seventeenth day (Haematoxylin and eosin, × 100)

FIG 29—Newly formed epithelium resurfacing a scald under a thin scab Section of the membrane removed from the surface of a buttock 16 days after scalding (Haematoxylin and eosin, × 100)

coagulated necrotic dermis This is invaded by masses of polymorphs 2 or 3 days after burning and a zone full of leucocytes then demarcates the coagulated slough The deeper viable parts of the follicles and sweat ducts often become hyperplastic but surface spreading is impossible until all the slough separates 10–20 days after burning. In biopsies removed before separation of the slough abortive horizontal spreading of epithelium beneath the slough may be found Occasionally the slough is invaded or even covered by a small amount of newly grown epithelium which will be lost when the slough separates



(a) (b)

FIG. 33 —Granulating whole skin-loss burn excised 23 days after burning. (a) Vascular cellular and oedematous granulation tissue growing from the subdermis towards the surface × 110 (b) Higher power view of a different microscopic field × 190 (Haematoxylin and eosin.)

When separation occurs resurfacing proceeds as described but the process is somewhat slower The new epidermis now develops from fewer islands of epithelium because the follicles and sweat coils which were inserted less deeply in the dermis have sloughed In the deepest kinds of partial skin loss burns all the follicles and many or most of the sweat coils are destroyed and resurfacing is entirely dependent on the most deeply situated sweat ducts or possibly from sweat coils

Connective tissue —A cellular vascular tissue resembling granulation tissue grows into the dermis from the subcutaneous tissue It grows obliquely upwards and is often found around viable sweat coils and new formed ducts or follicles Lymphocytic cuffing of these is often a

partly digested Many of the loosened abnormal collagen fibres are shed with the surface exudate but others may be incorporated in the new dermis They are distinguished by their strongly eosinophilic, partly refractile, sharp appearance and look somewhat like elastic fibres (Fig 34) Epithelialization of the new surface proceeds as previously described and final healing is delayed perhaps a few days the spreading epithelium may invade the necrotic collagen in

FIG 32 —Resurfaced partial skin-loss burn excised on twenty-second day Epithelialization was somewhat delayed because of the depth of the burning and immature epidermis covers the whole surface of the burn Note the irregular tongue-like downgrowths of hyperplastic epithelium invading the dermis from the epidermis (mainly left half of illustration) as well as the pre-existing sweat coils which have become hyperplastic and almost solid (right of illustration) (Haematoxylin and eosin, × 43)

places and may even spread on its surface Healing is accompanied by some ingrowth of young fibroblasts, capillary buds and lymphocytes often around hair follicles and sweat ducts Reconstitution of the upper dermis continues after resurfacing has been completed and reticulin and collagen fibres are laid down The new tissue can be distinguished histochemically by its high content of alkaline phosphatase (Fell and Danielli, 1943) as well as by the epithelial connections with the deep surface of the epidermis

Deep partial skin-loss burns —The dermis is heat-coagulated to a variable depth and deep to this there is a narrow zone of non-

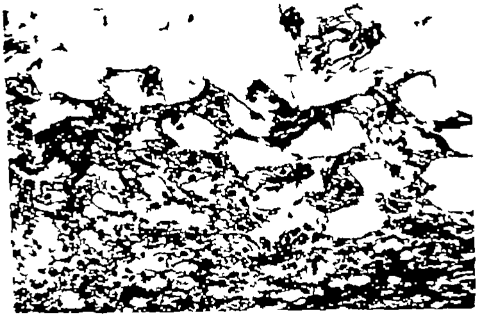


FIG. 35.—Regrowth of subcutaneous fat in a deep granulating burn. Note the appearance of foam cells, presumably developing lipoblasts, in the connective tissue adjacent to the fat cells. (Haematoxylin and eosin × 320.)

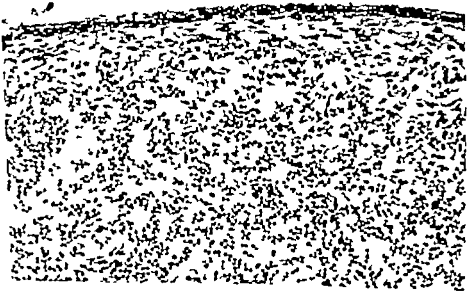


FIG. 36. Burn of arm excised after 8 weeks. Thin immature epithelium has spread over the surface of a granulating burn from the viable edge of epidermis (not visible). (Haematoxylin and eosin × 175.)

feature The epithelium spreads over a changed dermis, partly composed of old collagen and partly of young vascular connective tissue The dermis thickens after resurfacing is completed and maturation of the connective tissue follows The new dermis differs from that found in normal skin, the papillary layer is absent at first or poorly formed and elastic tissue may not appear for months Histologically the dermis appears to thicken from the invasion of connective tissue deep to the slough, and if this is so the viable sweat ducts and follicles must grow upwards with the thickening dermis

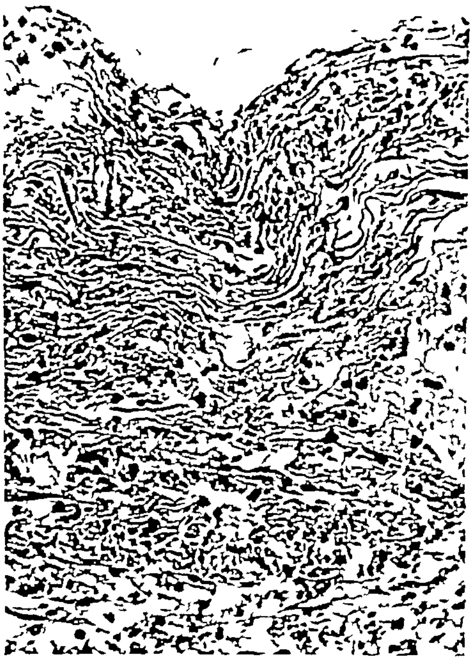


FIG 34 —Elastotically degenerated collagen fibres in the slough on the surface of a burn (Haematoxylin and eosin, × 270)

Later, nerves grow into the healed burn and nerve endings regenerate, hair follicles and glands often re-form but sometimes the area remains deficient in these structures

Whole skin-loss burns —Formation of the slough, its demarcation by leucocytes, its delayed separation and the invasion of the deeper part of the dermis by a vascular fibroblastic tissue rich in inflammatory cells takes place as described for the deepest kind of partial skin-loss burns The cellular exudate is particularly striking and is formed of migrating histiocytes, lymphocytes, often plasma cells which, together with the polymorphs and possibly eosinophil leucocytes which had already entered the area, make a varied cellular picture

Granulation tissue —The dermis begins to change 2–3 days after burning The deeper part is converted into a vascular, oedematous

than from hair follicles but in follicle free areas rich in sweat coils like the palm of the hand this is counterbalanced by the density of the ducts. The generalization of Converse and Robb-Smith (1944) that skin healed from sweat ducts is of poor quality has only a little truth

The thickness of the skin and the depth at which the coils and papil lae are placed also influence the outcome of burning For example skin is thin on the back of the hand and burns of a depth which elsewhere would leave many ducts and follicles viable and which would heal well, in this situation often heal relatively slowly and skin of poor quality and texture is formed In contrast burns on the face palm and sole deep enough to be whole skin loss elsewhere often regenerate quite well because many of the sweat coils are placed in the subcutaneous fat and not only in the dermis Analgesic burns in such areas are often partial skin loss in depth unlike analgesic burns in other areas.

LOCAL TREATMENT

Many recommended local applications have been found to delay healing and as yet, no agent capable of speeding epithelialization has been found It is now known that the formerly favoured tannic acid may increase the depth of necrosis delay the separation of the slough and possibly transform a partial skin loss burn into one involving the full thickness of the skin (Cannon and Cope 1943 Cameron Milton and Allen 1943 Brush Lam and Ponka 1947) Other tanning agents are likely to have similar properties For example the mild tanning substance Neosyn which was recom mended as a local application was investigated and was found to delay the healing of partial skin loss burns as well as having other potentially toxic properties (Bull and his colleagues 1954) Many agents with antibacterial properties including sulphanilamide propamidine dibromopropamidine proflavine gentian violet, triple dye as well as silver nitrate and other compounds, have an adverse effect on skin and other tissues and may interfere with normal healing either by increasing the depth of skin necrosis, by a toxic action on muscle fibres, by killing leucocytes or by inhibiting the migration of epithelium or by a mixture of these effects (Glynn 1941 Cannon and Cope 1943 Allen Burgess and Cameron 1944 Brush, Lam and Ponka 1947 Cruickshank and his colleagues 1955) Moreover locally applied toxic substances may be absorbed into the general circulation and it is in this way that tannic acid may produce serious damage to the liver (Chapter 22)

Tissue culture experiments indicate that among the least toxic

and cellular granulation tissue which soon invades the whole burned skin except the separating slough and may incorporate heat-altered but non-coagulated collagen fibres The capillary buds make their way vertically or obliquely to the surface whilst the fibroblasts, and later the new reticulin and collagen fibres, become arranged in rows more or less parallel to the surface In small experimental burns of the rat, vascular regeneration was found to be complete 12–16 days after injury and to have preceded completion of collagen fibre formation (Hughes and Dann, 1941) Often an excessive amount of granulation tissue forms because the restraining influence of a surface epidermis is absent

Subcutaneous fat —Reconstitution of the fatty layer is poor once destroyed by burns but it may occur by the metaplastic growth of connective-tissue cells in the fascia to lipoblastic foam cells (Fig 35)

Effects of severe infection —In some patients granulation tissue is poor, delayed or even absent This can be due to severe local infection and histologically the remains of the dermis and subcutaneous fat may be infiltrated with numerous leucocytes with minute abscesses in many places Poor granulation tissue may also result from severe systemic illness such as pneumonia or septicaemia

Contraction —Epidermal healing can only take place by migration of epithelium from the edge If the burn is small complete surface cover may occur, but if the burn is large epithelial cover may take months or may be impossible Meanwhile the granulating burn contracts, partly because the collagen collar around it shortens, and partly through contraction of the fibrosing granulation tissue The process ends in a dense irregular contracted scar

FACTORS INFLUENCING THE HEALING OF BURNS

In addition to the depth and quality of necrosis the main factors influencing the healing of burns are (1) site of burning, (2) bacterial infection (Chapter 6), (3) local therapy including, (4) skin grafting and (5) nutrition

SITE OF BURNING

Although a comparative study of burn healing in different areas between males and females at different ages has not been made (and would be very difficult) it is recognized that regeneration of burns in areas rich in hair follicles such as partial skin-loss burns of the scalp heal quickly and well Partial skin-loss burns in furry animals also heal quickly Regeneration from sweat ducts is probably less rapid

the graft has to be closely applied to the recipient bed Histologically changes take place in the graft recipient area and at their junction The bleeding surface of the bed clots and this fibrinous network mixed with red cells is rapidly infiltrated by leucocytes and later by capillary buds and fibroblasts Vascular connexion between the graft and its bed commences at about 48 hours, is followed or ac companied by fibroblastic invasion and is established at 7–10 days Collagenization of the junction follows The collagen fibres of the grafted dermis are sharply demarcated at first from the deeper granulation tissue of the bed but later the dermis is invaded and its collagen may be gradually replaced Changes occur in the epithelium of the graft exfoliation is associated with hypertrophy and thicken ing of the epidermis The stratum granulosum and the stratum corneum become thick and prominent and the latter may peel 7–10 days after application of the graft. Gibson and Medawar (1943) found that desquamation and restratification of the whole thickness of the epidermis occurred in areas and that the desquamating epidermis was separated from the underlying hyperplastic epidermis by small blisters containing leucocytes The epidermal hyperplasia is accompanied by acanthosis which according to Gillman and his colleagues (1953–54) sends epithelial downgrowths into the graft dermis and may even invade the recipient bed According to them the spurs of epithelium may be cut off from the epidermis then cornify and provoke a vigorous round-cell reaction in their vicinity At the edge of the graft epithelium loosely infiltrated with poly morphs grows outwards over the ungrafted granulating surface while epithelial invasion into the granulation tissue may give rise to small epidermic cysts Contact between the keratin at the edge and neighbouring dermis provokes a foreign body reaction

Factors influencing the take of autografts—The manner and the success of grafting are influenced by the age and character of the granulating bed and by infection Plastic surgeons have long known that old exuberant granulation tissue should be excised before applying a graft Presumably this is advisable because the growth of new granulation tissue under the graft induces a more ready vascular ization of the graft dermis It may also stimulate the growth of the graft epidermis and epithelial invasion of the graft as suggested by Gillman and his colleagues The successful take of grafts is often endangered or prevented by colonization of the skin by bacteria In particular *Streptococcus pyogenes* and *Pseudomonas pyocyanea* often prevent successful grafting or reduce the area of take and *Staphylococcus aureus* has a similar but less important effect (Chapter 6)

agents are important antibiotics like penicillin aureomycin streptomycin and polymyxin (Cruickshank and Lowbury. 1952)

Artificial digestion of burn slough—This has been attempted in order to reduce operative trauma, permit early skin grafting and thereby prevent infection Proteolytic and fibrinolytic agents of bacterial origin such as streptodornase and streptokinase have been unsuccessful in digesting heat-*coagulated* collagen (Connell and Rousselot. 1950) and the efficacy claimed for bacterial collagenases derived from *Clostridium welchii* and *Cl histolyticum* (Altemeier. Coith and Tytell. 1950) has not been satisfactorily demonstrated The ineffectiveness of these substances is not surprising, since pathologists have long known that this kind of coagulation is resistant to digestion by pus cells and contaminating bacteria Indeed it is for this reason that the slough does not liquefy *in situ* Some of the clinical successes claimed are probably the result of digesting non-coagulated necrotic skin which anyway would have been broken up by the normal leucocytic exudate

The claim that local injection or surface application of pyruvic acid aids the normal separation of slough (Harvey, 1950) is also not properly substantiated

SKIN GRAFTING

Grafting is necessary for all full-thickness skin-loss burns irrespective of size The ultimate purpose of grafting is to restore skin of a quality approaching that of normal skin, but the *immediate* purpose in patients with large whole skin-loss burns is to save life The grafted skin becomes a dressing which prevents exudation from the burn, and deters infection from without with its attendant risks and complications In addition skin grafting cuts short the period of anaemia, possibly shortens the katabolic response reduces the amount of scarring and degree of ultimate contracture boosts the patient's morale and in general hastens recovery and convalescence

Split-skin autografts—Split-skin grafts are thin portions cut from normal skin (donor area) and consist of epidermis with a variable thickness of dermis Only autografts which are cut from the patient's own skin are permanently acceptable to the recipient areas *homografts* which come from another person take temporarily but later disintegrate (*see* page 70)

The successful take of a split-skin autograft is finally dependent on its vascularization from the underlying bed but before this occurs its continued viability depends on tissue exudation for nutrition Thus

its lose weight and have an excessive protein kata negative nitrogen balance until the skin is healed grafting (Chapter 17) Peters (1945) suggested that the sis may result from the demands of the burned area for o-acids required for healing of the skin He thought en loss after burning may be due to the raiding of the of protein for one or more essential amino-acids, with limination of the remaining nitrogen from other un of the protein molecule

ie was added to the diet of burned rats in the hope that it e tissue breakdown and the negative nitrogen balance itial encouraging experiments it was found to be without t and Peters, 1945 Gribble Peters and Wakelin 1947) s the concept may still be of value in relation to other s or other constituents of cellular structure

REFERENCES

Burgess, F and Cameron G R. (1944) *J Path Bact.*, **56**, 217
V A Coith, R. L. and Tytell A. A. (1950) In *Symposium on Burns* 0 Washington National Research Council.
Lam, C R. and Ponka J L. (1947) *Surgery* **21** 662.
and Lennard-Jones J E. (1949) *Clin Sci* **8**, 155
D McG Ricketts, C and Sevitt, S (1954) *Unpublished report to dical Research Council*
G R Milton, R F and Allen J W (1943) *Lancet* **2**, 179
and Cope O (1943) *Ann Surg* **117** 85
P and Gorer P (1956) *Proc R Soc Med.*, **49** 117
L Gibson, T and Todd, J P (1945) In *Studies of Burns and Scalds* Medical Research Council Special Report Series No 249
F., and Rousselot, L. M (1950) In *Symposium on Burns* page 158 ington National Research Council.
J M and Rapaport, F T (1956) *Ann. Surg.*, **143**, 1956
bb-Smith, A H T (1944). *Ibid.*, **120**, 873
H D, Joslin, D Rees, T D and Stark, R B (1952) *Plast Reconstr* 9 557
R R A Bedford D and Rouillard, L M (1956) *Lancet* **1** 461
Langohr J L. Moore, F D., and Webster R C (1947) *Ann Surg*

., and Peters, R. A (1945) *Lancet* **1** 266.
k C N D., Jackson, D McG., Lowbury E J L Sevitt, S and E (1955) *Brit J plast Surg.*, **7** 320
bury E J L (1952) *Brit med J* **2**, 1070
., Fell, H B and Kodicek, E (1945) *Brit J exp Path* **26**, 367
(1832) *Lecons orales de Clinique Chirurgicale* vol. 1 pp 413 422. ermer Balliere.
d Danielli, J F (1943) *Brit J exp Path.* **24** 196
l Brown, A. (1945). In *Studies of Burns and Scalds*, page 49 l Council Special Report Series No 249
l [redacted] r **77** 299
Roux, M (1953-54) *Brit J plast Surg.*,

agents are important antibiotics like penicillin, aureomycin, streptomycin and polymyxin (Cruickshank and Lowbury, 1952)

Artificial digestion of burn slough —This has been attempted in order to reduce operative trauma, permit early skin grafting and thereby prevent infection Proteolytic and fibrinolytic agents of bacterial origin such as streptodornase and streptokinase have been unsuccessful in digesting heat-*coagulated* collagen (Connell and Rousselot, 1950) and the efficacy claimed for bacterial collagenases derived from *Clostridium welchii* and *Cl histolyticum* (Altemeier, Coith and Tytell, 1950) has not been satisfactorily demonstrated The ineffectiveness of these substances is not surprising, since pathologists have long known that this kind of coagulation is resistant to digestion by pus cells and contaminating bacteria Indeed it is for this reason that the slough does not liquefy *in situ* Some of the clinical successes claimed are probably the result of digesting non-coagulated necrotic skin which anyway would have been broken up by the normal leucocytic exudate

The claim that local injection or surface application of pyruvic acid aids the normal separation of slough (Harvey, 1950) is also not properly substantiated

SKIN GRAFTING

Grafting is necessary for all full-thickness skin-loss burns irrespective of size The ultimate purpose of grafting is to restore skin of a quality approaching that of normal skin, but the *immediate* purpose in patients with large whole skin-loss burns is to save life The grafted skin becomes a dressing which prevents exudation from the burn, and deters infection from without with its attendant risks and complications In addition skin grafting cuts short the period of anaemia, possibly shortens the katabolic response, reduces the amount of scarring and degree of ultimate contracture, boosts the patient's morale and in general hastens recovery and convalescence

Split-skin autografts —Split-skin grafts are thin portions cut from normal skin (donor area) and consist of epidermis with a variable thickness of dermis Only autografts which are cut from the patient's own skin are permanently acceptable to the recipient areas *homografts* which come from another person take temporarily but later disintegrate (*see* page 70)

The successful take of a split-skin autograft is finally dependent on its vascularization from the underlying bed, but before this occurs its continued viability depends on tissue exudation for nutrition Thus

homografts by Gibson and Medawar (1943) indicated that vascularization of the homodermis is present by the fifth day A cellular reaction is provoked in the recipient bed although there is little or no cellular infiltration of the graft and during the third or fourth week the graft epidermis becomes necrotic The vascular beds of autotransplants and homotransplants were compared by Taylor and Lehrfeld (1953) with a skin microscope In both a circulation was established by the fourth day apparently because capillary sprouts from the host tissue connected with the vascular network of the graft dermis Capillary stasis was present on the eighth day even though the homograft itself looked healthy The cessation of capillary flow which possibly resulted from a progressive leakage of fluid by the capillaries was soon followed by multiple small haemorrhages into the graft The epidermis now loosened and was easily separated Similar studies in man by Converse and Rapaport (1956) confirmed the early vascularization of the graft but these are in contrast to the results of Conway and his colleagues (1952) who failed to find a homodermal circulation The work of the latter writers may be criticized, however on technical grounds since the skin chamber method used may have interfered with graft take The fate of the homodermis varies if it becomes covered with auto-epidermis spreading from nearby skin it is clinically incorporated in the skin Histologically it is invaded by tissue cells and finally replaced by autocollagen the homocollagen may be broken up and phagocytosed in part or become splayed out, eroded and disappear If it does not become covered by auto-epidermis the homodermis separates a week or so after the loss of the homo-epidermis and is lost Whilst it remains the granulation tissue does not hypertrophy

Pathogenesis of graft death and immune reactions—The work of Gibson and Medawar indicates that death of the homograft epidermis is humoral and not cellular in origin (Gibson and Medawar 1943 Medawar 1944) They postulated that the homograft provokes a tissue immunity and that an antigen-antibody reaction in the epidermis takes place with consequent death of the latter This concept explains the initial take and the latent period of 2–4 weeks before epidermal necrosis occurs and it also explains why subsequent homografts from the same donor break down more rapidly than the first Various observations, including those of Taylor and Lehrfeld (1953) however suggest that the first effect of the humoral agent may be on the vessels of the homodermis An increased capillary permeability occurs producing local oedema, and capillary stasis follows It is not certain however whether these changes

The failure of graft-take may be part of a vicious circle bacterial infection persists because the burn wound is not closed, and it cannot be closed because it is infected Antibiotic therapy often plays a valuable part in breaking this circle

Autografting small and large burns —The modern tendency of surgery is to graft whole skin-loss burns as early as possible When the burn is small, primary excision of the necrotic skin and immediate grafting can be effectively performed within 24–48 hours of burning Some surgeons carry out immediate grafting on larger burns such as those involving up to 10 per cent of the body area

It is usual to delay grafting for 2–3 weeks in patients with extensive burns necessitating early plasma transfusion By this time the "shock period" is over, the partial skin-loss areas have healed or almost healed and the whole skin-loss burns are sloughing or granulating Unfortunately many of these patients have become seriously ill and have a poor prognosis A case can be argued for primary excision and grafting of large whole skin-loss burns such as burns involving 40 per cent or more of the body area within a day or two of burning As the prognosis of such extensively burned patients is not good (Chapter 8) the danger of an early extensive operation may be outweighed by the advantage of a reduced wound size Transfusion with blood and plasma before, during and after the operation has to be carefully controlled Successful grafting of even half of a 50 per cent whole skin-loss burn transforms it in effect to a 25 per cent whole skin-loss wound and the patient's prognosis may be much improved if he survives the first few days A clinical trial of primary excision and grafting large whole skin-loss burns is in progress at the Birmingham Accident Hospital (Jackson, 1955–57)

Homografts —Although skin grafts from another person take only temporarily they have a place in the treatment of patients with extensive burns The grafts take for about 2–4 weeks, during which the epidermis remains viable and acts as a relatively waterproof dressing A clinical study of the use of split-skin homografts for burns was reported by Jackson (1954), who concluded that the grafts reduced the size of the wound with the least disturbance to the patient, and that during their period of take they reduced fluid and protein loss, limited infection, relieved pain and made dressings less uncomfortable

The series of events preceding the destruction of the homograft have been studied by Gibson and Medawar (1943), Conway and his colleagues (1952), Taylor and Lehrfeld (1953) and Converse and Rapaport (1956) Careful histological comparison of human autografts and

Burned patients lose weight and have an excessive protein katabolism and a negative nitrogen balance until the skin is healed naturally or by grafting (Chapter 17) Peters (1945) suggested that the tissue proteolysis may result from the demands of the burned area for essential amino-acids required for healing of the skin He thought that the nitrogen loss after burning may be due to the raiding of the tissue stores of protein for one or more essential amino-acids with consequent elimination of the remaining nitrogen from other unwanted acids of the protein molecule

Methionine was added to the diet of burned rats in the hope that it would reduce tissue breakdown and the negative nitrogen balance but, after initial encouraging experiments it was found to be without effect (Croft and Peters 1945 Gribble Peters and Wakelin 1947) Nevertheless the concept may still be of value in relation to other amino-acids or other constituents of cellular structure

REFERENCES

Allen, J W Burgess, F and Cameron, G R. (1944) *J Path. Bact* 56, 217
Altemeier W A., Coith, R. L., and Tytell, A. A (1950). In *Symposium on Burns* page 160 Washington National Research Council.
Brush, B E. Lam, C R. and Ponka, J L. (1947) *Surgery* 21 662.
Bull, J P and Lennard Jones, J E. (1949) *Clin Sci.*, 8, 155
— Jackson, D McG Ricketts, C and Sevitt, S (1954) *Unpublished report to the Medical Research Council*
Cameron, G R. Milton, R. F., and Allen, J W (1943) *Lancet* 2, 179
Cannon, B and Cope, O (1943) *Ann Surg* 117 85
Clarkson, P and Gorer P (1956) *Proc R. Soc Med.* 49 117
Colebrook, L. Gibson, T., and Todd J P (1945) In *Studies of Burns and Scalds* page 6. Medical Research Council Special Report Series No 249
Connell, J F., and Rousselot L. M (1950) In *Symposium on Burns* page 158 Washington National Research Council
Converse, J M., and Rapaport, F T (1956) *Ann Surg* 143, 1956.
— and Robb-Smith, A H T (1944) *Ibid* 120 873
Conway H D Joslin D Rees, T D., and Stark, R. B (1952) *Plast Reconstr Surg* 9 557
Coombs, R R A Bedford, D and Rouillard, L. M (1956) *Lancet* 1 461
Cope, O., Langohr J L. Moore F D and Webster R. C (1947) *Ann Surg* 125, 1
Croft, P B., and Peters, R. A (1945) *Lancet* 1 266.
Cruickshank, C N D., Jackson, D McG Lowbury E J L., Sevitt, S and Topley E (1955) *Brit J plast Surg* 7 320
— and Lowbury E, J L. (1952) *Brit med. J.*, 2, 1070.
Danielli J F Fell, H B and Kodicek, E (1945) *Brit J exp Path* 26, 367
Dupuytren G (1832) *Lecons orales de Clinique Chirurgicale* vol. 1 pp 413 422. Paris Germer Bailliere
Fell, H B and Danielli, J F (1943) *Brit J exp Path* 24 196.
Gibson, T and Brown, A. (1945) In *Studies of Burns and Scalds* page 49 Medical Research Council Special Report Series No 249
— and Medawar P B (1943) *J Anat* 77 299
Gillman, T Penn J Bronks, D and Roux, M (1953 54). *Brit J plast Surg* 6, 153
— — — — (1955) *Brit J Surg* 43, 141

produce the graft necrosis or whether they result from primary necrotizing changes in the graft. The tissue sensitivity is not unlike that provoked by the tubercle bacillus. Irregular antibodies are rarely if ever detected in the recipient's serum but this may be due to the limitations of present-day technique: the demonstration by Coombs, Bedford and Rouillard (1956) of specific mixed agglutination between epidermal cells and blood cells has opened up new possibilities.

An immune antibody might be produced in the recipient's plasma by red blood cells of the donor contained within the homograft. Clarkson and Gorer (1956) found an irregular antibody in the serum of a child active against her father's red cells; she had been burned and homografted with her father's skin. The nature of the antibody was not determined but it was not an anti-D antibody nor within the ABO system. This kind of immunization seems to be rare, but its incidence and the conditions under which it develops require investigation. In the meantime Rhesus-negative (D negative) recipients should be homografted with skin from Rhesus-negative donors otherwise the important anti-Rhesus (anti-D) antibody might develop. This is particularly important for girls and women of the child-bearing age where the existence of these antibodies can bring about erythroblastosis foetalis. Furthermore, the possibility that an irregular antibody may be present in the serum of a homografted patient requiring a blood transfusion later should be borne in mind by the pathologist. The crossmatching should include the additional precaution of an indirect antiglobulin (Coombs') test normally adopted for previously transfused patients.

NUTRITION

In a study of the healing process in experimental burns, Kozdoba (1942) showed that adequate nutrition was important. In particular avitaminosis or hypovitaminosis C in guinea-pigs was found to delay healing considerably. The burns showed thick necrotic masses on the surface deep to which the granulation tissue was poorly developed. The utilization of ascorbic acid in the healing burn is known to be high because the vitamin is essential for phosphatase activity and maturation of collagen in healing wounds (Danielli, Fell and Kodicek, 1945). This suggests that the ascorbic acid requirement of a burned patient is greater than normal and that vitamin C therapy may be of value (*see* Chapter 17).

Kozdoba also found that lack of vitamin A was associated with slower cicatrization, abnormal epithelialization and a longer healing time.

Burned patients lose weight and have an excessive protein katabolism and a negative nitrogen balance until the skin is healed naturally or by grafting (Chapter 17) Peters (1945) suggested that the tissue proteolysis may result from the demands of the burned area for essential amino-acids required for healing of the skin He thought that the nitrogen loss after burning may be due to the raiding of the tissue stores of protein for one or more essential amino-acids with consequent elimination of the remaining nitrogen from other unwanted acids of the protein molecule

Methionine was added to the diet of burned rats in the hope that it would reduce tissue breakdown and the negative nitrogen balance but, after initial encouraging experiments it was found to be without effect (Croft and Peters, 1945 Gribble Peters and Wakelin 1947) Nevertheless the concept may still be of value in relation to other amino-acids or other constituents of cellular structure

REFERENCES

Allen, J W., Burgess, F and Cameron, G R. (1944) *J Path Bact* 56 217

Altemeier W A. Coith R. L., and Tytell, A A. (1950) In *Symposium on Burns* page 160 Washington National Research Council.

Brush, B E., Lam, C R., and Ponka J L. (1947) *Surgery* 21 662.

Bull, J P and Lennard Jones, J E. (1949) *Clin Sci.*, 8, 155

— Jackson, D McG Ricketts, C and Sevitt, S (1954) *Unpublished report to the Medical Research Council*

Cameron, G R., Milton, R. F., and Allen, J W (1943) *Lancet* 2, 179

Cannon, B., and Cope, O (1943) *Ann Surg.*, 117 85

Clarkson, P and Gorer P (1956) *Proc R. Soc Med* 49 117

Colebrook, L., Gibson, T and Todd, J P (1945) In *Studies of Burns and Scalds* page 6. Medical Research Council Special Report Series No 249

Connell J F., and Rousselot, L. M (1950) In *Symposium on Burns* page 158 Washington National Research Council.

Converse, J M and Rapaport F T (1956) *Ann Surg* 143, 1956.

— and Robb-Smith, A. H T (1944) *Ibid* 120 873

Conway H D Joslin, D Rees, T D and Stark, R. B (1952) *Plast Reconstr Surg* 9 557

Coombs, R. R. A Bedford D and Roulllard, L. M (1956) *Lancet* 1 461

Cope O Langohr J L., Moore F D and Webster R C (1947) *Ann. Surg* 125 1

Croft, P B and Peters, R. A (1945) *Lancet* 1 266.

Cruickshank, C N D., Jackson, D McG., Lowbury E. J L., Sevitt S and Topley E. (1955) *Brit J plast Surg.*, 7 320

— and Lowbury E. J L. (1952) *Brit med J* 2, 1070

Danielli, J F Fell, H B and Kodicek E. (1945) *Brit J exp Path.* 26, 367

Dupuytren, G (183?). *Lecons orales de Clinique Chirurgicale* vol. 1 pp 413 422. Paris Germer Balliere

Fell H B and Danielli, J F (1943) *Brit J exp Path.* 24, 196

Gibson, T and Brown, A (1945) In *Studies of Burns and Scalds* page 49 Medical Research Council Special Report Series No 249

— and Medawar P B (1943) *J Anat* 77 299

Gillman, T., Penn, J., Bronks, D and Roux, M (1953–54) *Brit J plast Surg* 6, 153

— — — (1955) *Brit J Surg* 43, 141

Glynn, L E (1941) *J Path Bact*, **53**, 183
Gordon, J, Hall, R A, Heggie, R M, and Horne, E A (1946) *J Path Bact*, **58**, 51
Gribble, M deG, Peters, R A, and Wakelin, R W (1947) *J Physiol*, **106**, 36
Harvey, S C (1950) In *Symposium on Burns*, page 151 Washington, National Research Council
Hughes, A F W, and Dann, L (1941) *Brit J exp Path*, **22**, 9
Jackson, D McG (1953) *Brit J Surg*, **40**, 588
— (1954) *Brit J plast Surg*, **7**, 26
— (1955–57) Personal communication
Kozdoba, A Z (1942) *Khirurgia*, No 10, 52
Medawar, P B (1944) *J Anat*, **78**, 176
Patey, D H, and Scarff, R W (1944–45) *Brit J Surg*, **32**, 32
Peters, R A (1945) *Brit med Bull*, **3**, 81
Sevitt, S (1949) *J Path Bact*, **61**, 427
Taylor, A C, and Lehrfeld, J W (1953) *Plast Reconstr Surg*, **12**, 423
Unna, P G (1896) *Histopathology of the Diseases of the Skin* Edinburgh
Wiseman, R (1676) *Severall Chirurgicall Treatises* London (Quoted by Jackson, 1953)

CHAPTER 5

SKIN COMPLICATIONS AND SEQUELAE

THE complications and sequelae in the skin after burning are (1) infection (*see* Chapters 6 and 7) (2) scars and contractures (3) hypertrophic scars and keloids and (4) malignant tumours

SCARS AND CONTRACTURES

AFTER WHOLE SKIN-LOSS BURNS

Scarring which may lead to ugly contractures, deformities of joints and limitation of movement, occurs after whole skin loss burns which heal spontaneously The size of the chronic granulating wound is slowly reduced by a progressive contraction of the collagen collar around it, and this process is aided by a contraction of the maturing scar tissue within the burn Loss of skin surface that is skin shortage results and on a flat surface this amounts to 20 per cent or more in deep burns

The epithelium covering the scar is generally of poor quality having finally and slowly spread over the granulating surface from the edge aided perhaps by growth from a few deeply situated sweat coils The epidermis is often thin (Fig 37) and dry but sometimes it is hypertrophic hyperkeratotic and liable to flake (Fig 38) It is easily cracked or ulcerated by trauma to which it is frequently subjected when the scar is elevated or adherent to deep structures. At first the scar is red but later it becomes poorly vascularized because the dense fibrous tissue replacing the dermis obliterates many blood vessels. The abnormal dermis is devoid of hair and glands it is inelastic and lacks normal suppleness it is generally thicker than normal and is often adherent to the deeper structures

In whole skin-loss burns chronic hypertrophic granulation tissue is the origin of the scar tissue The granulations hypertrophy because the normal restrictive influence of the epithelial surface is absent thus early skin grafting often prevents or considerably reduces the degree of scarring and contracture

Intermittent tension and movement of the healing area may contribute to an increase in scar tissue For example a burn behind the knee on the front of the neck or in other flexures will be

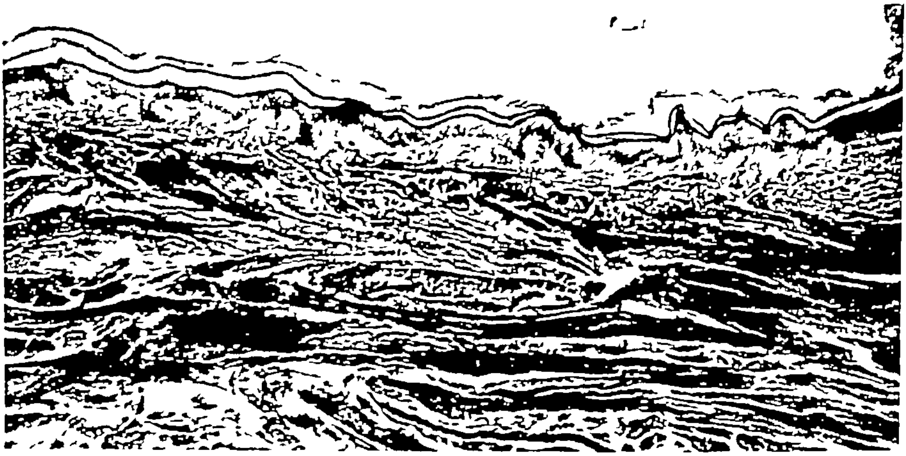


FIG 37 —Burn scar 2½ years after injury Broad hyalinized fibres traverse the thickened dermis, there are no follicles or sweat coils, blood vessels are few, the papillary layer is poorly formed and the covering epidermis is thin (Haematoxylin and eosin, × 35)

intermittently stretched and cords of fibrous tissue covered by flaky epithelium may develop along the lines of tension The increased scarring is presumably from intermittent injury to fibrosing dermis as a result of which new fibrous tissue is progressively added

AFTER PARTIAL SKIN-LOSS BURNS

Some skin shortage may also occur during the healing of partial skin-loss burns even though there is little or no scarring The dermis between the regenerating islands of epithelium contracts but the

FIG 38 —Burn scar of foot covered by hyperplastic hyperkeratotic and acanthotic epidermis (Haematoxylin and eosin, × 35)

amount of contracture is much less than is found in deep burns (Converse and Robb-Smith 1944) The shortage of skin may be noticeable in regions where the skin is not loose such as over the extensor surface of joints on the dorsum of the hands and in the eyelids where ectropion may result. Contraction and shortage of skin is greater following deep partial skin loss burns and scarring may develop In such burns epithelialization is delayed by a slough and infection may further delay resurfacing Because the epithelial surface is delayed an excessive amount of new vascular connective tissue forms and this may finally mature into scar tissue Sometimes a considerable fibrosis of the area results which may invade the subcutaneous tissue

COMPLICATIONS

Some scars become itchy or painful Repeated trauma may produce fissures or even ulcers and these may become infected and heal with difficulty Occasionally the fibrous tissue becomes irregularly calcified The major complications are scar hypertrophy keloids and malignant tumours

HYPERTROPHIC SCARS AND KELOIDS

Scars sometimes hypertrophy during or soon after the course of healing of a burn and particularly in slow healing partial skin loss burns In addition to being raised and hypertrophied, they differ from normal scars in that they remain pink or red for a long time and commonly burn or itch The hypertrophic state lasts for months or years, after which the scar slowly regresses and becomes thin white and flat Scar hypertrophy is more likely to develop in children and young women

True keloids are at first indistinguishable from hypertrophic scars but unlike the latter they tend to spread into the surrounding skin and do not regress

HISTOLOGY

In the early stage of scarring the dermis is thick and relatively vascular the collagen fibres are excessive and are mostly parallel to the skin surface The fine papillary layer and elastica are absent Sometimes the dermal surface is smooth and is covered by thin epithelium without rete pegs and sometimes the epithelium shows acanthotic downgrowths Later the collagen fibres increase in diameter and the dermis becomes a thick layer of broad and finally hyalinized fibres During the stage of regression the vascularity decreases, the fibres progressively shrink and elastica is said to re appear (Glucksmann 1951)

FIG 37 —Burn scar 2½ years after injury Broad hyalinized fibres traverse the thickened dermis, there are no follicles or sweat coils, blood vessels are few, the papillary layer is poorly formed and the covering epidermis is thin (Haematoxylin and eosin, × 35)

intermittently stretched and cords of fibrous tissue covered by flaky epithelium may develop along the lines of tension The increased scarring is presumably from intermittent injury to fibrosing dermis as a result of which new fibrous tissue is progressively added

AFTER PARTIAL SKIN-LOSS BURNS

Some skin shortage may also occur during the healing of partial skin-loss burns even though there is little or no scarring The dermis between the regenerating islands of epithelium contracts but the

FIG 38 —Burn scar of foot covered by hyperplastic, hyperkeratotic and acanthotic epidermis (Haematoxylin and eosin, × 35)

but remain trapped in the dermis where they act as intrinsic foreign bodies Glucksmann s interpretation of the dermal epithelial foci was criticized by Gillman and his colleagues (1953–54) They found foci of epithelium surrounded by collections of inflammatory cells within the dermis of healing split skin graft donor areas but con sidered that they were derived from the regenerating epidermis. According to them the latter sends epithelial spurs into the upper dermis some of which become isolated and cornify Gillman and his colleagues suggested that the keratin and epithelial elements described by Glucksmann were part of the normal process of healing and were derived from the epidermis and not from dislocated or displaced dermal epithelial elements

Systemic factors.—Certain groups of people such as Negroes are more prone to scar hypertrophy than others, and the susceptibility extends to particular individuals and families (Jacobsson 1948) The condition is more common in females than in males, occurs frequently in girls with red hair or with fair complexions and is not uncommon in children It is rarely seen in elderly people Glucksmann (1951) and Mowlem (1951) suggested that the age and sex differences are related to the thickness and distribution of lanugo hairs

Some relationship with an endocrine imbalance is suggested by the work of Geschickter and Lewis (1935) who found a considerable concentration of oestrogens and pituitary hormones in keloids and this is supported by the experiments of Vargas (1943) who produced keloids in monkeys treated with oestrogens. Gillman and his col leagues suggested that the well known susceptibility of Negroes and coloured people may be related, not to an hereditary predisposition as is commonly believed but to the effects of chronic malnutrition which is endemic in the colonial and semicolonial territories of Africa and Asia. They point out that the liver is deranged in chronic malnutrition and, since the inactivation of oestrogens is a normal liver function a disturbance of the normal hormone balance may develop in chronically undernourished people This may contribute to the susceptibility of coloured people to keloids

Hypertrophic scarring was frequent among those who recovered from flash burns due to the atomic bomb explosions in Hiroshima and Nagasaki (Fig. 39) These scars have usually been called keloids but most of them regressed months or years later and others may still do so The liver-disorder hypothesis is applicable to the Japanese since both liver disease and malnutrition are common in Japan other explanations offered are inadequate early treatment (including unfavourable local applications) infection of the burns, the effects of

AETIOLOGY

The factors involved are local and systemic

Local factors—The local factors postulated are intermittent tension and movement of the skin (*vide supra*), a low-grade infection and the development of an atypical foreign body reaction Mowlem (1951) doubted whether thickening due to tension and movement or to delayed healing from infection is true scar hypertrophy but this may be a distinction with little difference

Foreign-body reaction—Glucksmann (1945, 1951) claims that hypertrophic scars are the result of a foreign-body reaction in the dermis

FIG 39—Hypertrophic scar resulting from a flash burn at Nagasaki The scar has a linear lower border because the patient, bathing at the time of the atom bomb explosion, was immersed up to the shoulder (Kusano, 1953)

usually related to dislocated hair fragments or follicles, cystic displaced sweat coils and other keratin debris, or alternatively to extrinsic foreign bodies like cotton wool fibres, dust and talcum powder added to the wound, or to both intrinsic and extrinsic foreign bodies According to him the scar hypertrophies when a foreign-body reaction appears from contact between the dermis and keratin, and the scar regresses when all the keratin is absorbed or removed by phagocytes This could explain, he says, why hypertrophic scars occur in skin which bears lanugo hairs Their follicles are weak, so that when cut across they are unable to grow through to the surface

in burn scars and that there was some pre-existing lesion in 45 per cent of the cases.

Malignant degeneration of burned skin may be classified into (1) acute wound cancer (2) chronic scar cancer and (3) sarcoma. The distinction between carcinoma in old burn scars and acute burn carcinoma occurring within a few months of burning was made originally by Treves and Pack (1930)

ACUTE BURN CANCER

The acute variety developed in 12 of the 73 cases of carcinoma following burns reviewed by Treves and Pack (1930) in 6 of their own 28 cases and in 19 of the 100 cases reviewed by Arndt (1933) it is therefore less common than chronic scar cancer The neoplasm develops in middle aged or elderly people usually within a year of burning—the mean age of the patients when burned was between 50 and 55 years and the average interval before the onset of malignant change was 4 months in Treves and Pack s cases and 11 months in those reviewed by Arndt Treves and Pack suggested that acute wound cancer develops in elderly people whose skin is already atrophic or keratotic and thereby predisposed to carcinogenic influences and that the thermal injury is the exciting agent

The majority of the tumours with a relatively rapid onset are basal cell carcinomas but about one third are squamous-cell neoplasms. Basal-cell tumours are more frequent possibly because the acute cancers seem to have followed partial skin loss burns which healed slowly or failed to heal completely but which did not destroy all the sweat glands and hair follicles

CHRONIC SCAR CANCER

There are numerous descriptions of carcinoma in old burn scars. The subject has been reviewed and groups of cases have been de scribed by Durand (1888) Johnson (1926) Mason (1929) Treves and Pack (1930) Arndt (1933) Glover and Kiehn (1949) Murakami (1949) Iiso (1950) and others

In most cases the burn seems to have involved the full thickness of the skin In many cases surface healing often took months and scars developed later these broke down and became malignant In some the burn never healed completely and the carcinoma developed years later in a chronic discharging area

Appearance and mode of onset —Two clinical varieties have been described Most of the carcinomas become flat indurated ulcers with raised or thickened edges thus resembling other skin cancers the remainder are bulky protruding papillary growths Multiple ulcer

irradiation by gamma and other rays and a "racial" predisposition of the Japanese.

MALIGNANT TUMOURS OF THE SKIN

The first major description of ulcer-cancer in old degenerating scars was that by the French surgeon Marjolin in 1828, hence Marjolin's ulcer, but his account was preceded by the report of the English surgeon Hawkins (1825), who described two cases of carcinoma in old burn scars. Carcinoma is now a recognized complication of chronic inflammation in skin due to lupus, psoriasis, arsenical dermatitis, osteomyelitic sinuses and other conditions, as well as in chronically unhealed skin and healed scars following burns.

The frequency of carcinoma after burning is impossible to determine but it cannot be high. Nevertheless Glover and Kiehn (1949) suggested that any burn scar which is subjected to continuous injury will eventually become malignant if the patient lives long enough, but this seems an overstatement. The over-all incidence among skin cancers of tumours originating in burned skin has been estimated by Treves and Pack (1930) in the U.S.A. and by Levi (1956) in Birmingham. Treves and Pack reported that 2 per cent of 1,091 squamous carcinomas and 0.5 per cent of 1,374 basal-cell tumours seen in their hospital developed in previously burned skin. Levi's findings are in agreement with the above: she analysed the skin cancers seen in the Birmingham United Hospitals between 1936 and 1949 and classified them into epitheliomas and rodent ulcers: 1.3 per cent of 699 epitheliomas and 0.7 per cent of 1,794 rodent ulcers originated in previously burned skin. On the other hand, Shrek (1941) estimated that as many as 18 per cent of all malignant skin tumours developed in scars from burns, lacerations, ulcers and other causes, but this seems very high. The over-all and regional skin incidence will not only vary with the frequency of carcinoma following pre-existing lesions other than burns but also with the location of burning, since some parts of the body are burned more frequently than others (hand, face, arm and leg) and some skin areas may be more prone to cancer than others. Mason (1929) reported that 7.4 per cent of 255 cases of carcinoma of the upper extremity developed in burn scars (excluding those which followed radium applications or x-radiation), and that 19.4 per cent of 98 cases of carcinoma of the hand following irritation or injury originated in burned skin. Taylor, Nathanson and Shaw (1941) found that 5.4 per cent of 430 epidermoid carcinomas of the limbs developed

in burn scars and that there was some pre-existing lesion in 45 per cent of the cases.

Malignant degeneration of burned skin may be classified into (1) acute wound cancer (2) chronic scar cancer and (3) sarcoma The distinction between carcinoma in old burn scars and acute burn carcinoma occurring within a few months of burning was made originally by Treves and Pack (1930)

ACUTE BURN CANCER

The acute variety developed in 12 of the 73 cases of carcinoma following burns reviewed by Treves and Pack (1930) in 6 of their own 28 cases and in 19 of the 100 cases reviewed by Arndt (1933) it is therefore less common than chronic scar cancer The neoplasm develops in middle aged or elderly people usually within a year of burning—the mean age of the patients when burned was between 50 and 55 years and the average interval before the onset of malignant change was 4 months in Treves and Pack s cases and 11 months in those reviewed by Arndt. Treves and Pack suggested that acute wound cancer develops in elderly people whose skin is already atrophic or keratotic and thereby predisposed to carcinogenic influences, and that the thermal injury is the exciting agent

The majority of the tumours with a relatively rapid onset are basal cell carcinomas but about one-third are squamous-cell neoplasms. Basal-cell tumours are more frequent possibly because the acute cancers seem to have followed partial skin loss burns which healed slowly or failed to heal completely but which did not destroy all the sweat glands and hair follicles

CHRONIC SCAR CANCER

There are numerous descriptions of carcinoma in old burn scars. The subject has been reviewed and groups of cases have been described by Durand (1888) Johnson (1926) Mason (1929) Treves and Pack (1930) Arndt (1933) Glover and Kiehn (1949) Murakami (1949) Tiso (1950) and others

In most cases the burn seems to have involved the full thickness of the skin In many cases surface healing often took months and scars developed later these broke down and became malignant. In some the burn never healed completely and the carcinoma developed years later in a chronic discharging area.

Appearance and mode of onset.—Two clinical varieties have been described Most of the carcinomas become flat indurated ulcers with raised or thickened edges thus resembling other skin cancers the remainder are bulky protruding papillary growths Multiple ulcer

cancers may form if the scarring is extensive The ulcers vary considerably in size some are small (2–3 centimetres in diameter) and involve only part of the scar, but if left untreated they may extend considerably over months or years Others are 10–20 centimetres in diameter and vast extensive cancers have been reported

The commonest sites are naturally those areas which are most commonly burned The hand, head, arm and leg are the usual sites, and when the hand is affected it is always the dorsum (Fig 40) Unlike the dorsum, burns of the palm—even deep burns—generally heal rapidly because the skin is thick and the sweat coils from which the epidermis regenerates are more deeply situated than in most other regions

The ulcer may begin in different ways it may start as a small itchy papule which increases in size and ulcerates, the ulcer then extends and becomes malignant if not already so, it may begin as a diffuse swelling of a hypertrophic scar which later breaks down and forms an ulcer, sometimes a scar becomes scaly and itchy, is excoriated by scratching and an ulcer develops, and sometimes cracks or fissures may form, heal, and break down repeatedly, but finally persisting and developing into a tumour

Histology—Most of the scar tumours are squamous-cell carcinomas (Fig 41) but a number of basal-cell tumours have been reported The squamous cancers are mostly well-differentiated neoplasms forming sheets of epidermoid tissue at least part of which is keratinized into horny pearls, but in a minority the epidermoid structure is poorly differentiated Silva (1947) reported 10 cases and remarked on the frequency of well-differentiated "spindle-cell" carcinomas Most of the basal-cell tumours are derived from the epidermis, but occasionally the tumour is partly or wholly a subepidermal growth of sweat-gland origin and part of it may have a syringomatous structure Another part of the basal-cell tumour depicted in Fig 42 was of this kind The connective scar tissue in the base of the ulcer is not invaded at an early stage It appears to restrict the deep spread of the growth and this is important because the tumour may remain localized for years

The site of biopsy should be chosen with care because the carcinomatous change may be restricted at first to a small part of the ulcer In some cases a number of biopsies have been required to prove malignancy

Spread—Invasion of the tissues deep to the scar is a late phenomenon but when it occurs the tumour grows rapidly, presumably because it passes from relatively avascular scar tissue to muscle and bone which

have a good blood supply Lymphatic spread is an even later phenomenon because the dense fibrous scar obliterates the lymphatic channels, and the neoplasm must penetrate to deep patent capillaries before metastases are possible When this occurs the regional lymph nodes become seeded with cancer cells and lymph gland secondaries rapidly develop

FIG 40

FIG 41

FIGS. 40 and 41 —Skin carcinoma after burning and grafting. A man of 63 years was burned by an incendiary bomb on the dorsum of the hand, the burn was excised and a split-skin graft was applied Eight and a half years later an ulcer formed and extended (Fig. 40) Six months afterwards he sought advice a biopsy established the diagnosis of squamous-cell carcinoma (Fig. 41) A part of the hand was amputated and there was no recurrence 6 years later (Fig. 41 haematoxylin and eosin × 54)

Blood borne spread is exceedingly uncommon and visceral metastases are rare

Pathogenesis.—Unlike acute burn cancer it is the age of the scar which is important and not the age of the patient when burned Analysis of 60 recorded cases shows that the scars varied from 4 to 69 years old before malignancy developed 83 per cent were older than 10 years, 50 per cent older than 30 years and 13 per cent were older

than 50 years The ages of the patients ranged from 19 to 84 years, 80 per cent were more than 40 years of age and 37 per cent were older than 60 years This is because of the long latent period necessary before there is a malignant change

Scar cancer has a preference for male skin, since 70–80 per cent of the cases occurred in males However the preference for male skin may be greater than this indicates because the majority of burned patients are females, particularly those who are burned in childhood The difference may be because the skin of most men, particularly of the hands, is exposed to greater trauma than the skin of women

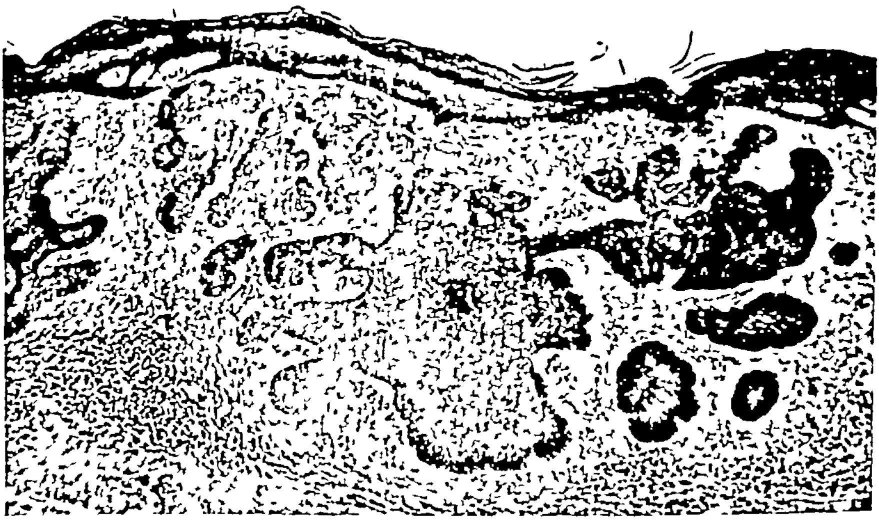


FIG 42—Basal-cell part of a mixed basal-cell–sweat-duct carcinoma on the site of a burn 15 years previously Patient was an elderly man and had a small ulcer on the back of the hand for 2 years Local excision and grafting, no recurrence 5 years later (Haematoxylin and eosin, × 52)

Chronic irritation—All workers agree that chronic irritation of the scarred skin predisposes to the malignant change Pruritus is a dangerous complication because it leads to scratching The delicate epithelium is easily injured and destroyed repeated injury is important because abrasions, fissures and ulcers form They heal with difficulty because they become infected and because the scar is poorly vascularized and the epidermis is imperfectly nourished In some patients a subsequent burn on the same area or x-irradiation of the chronic ulcer was followed by a malignant change

Dermal-epidermal relationship—The development of cancer in the *scarred* area suggests that the abnormal dermis plays an important role There is evidence that alterations in the dermis are important

or even essential for the development of experimental skin cancers and that changes in the epidermis alone cannot be responsible Carcinogenic agents do not appear to cause a direct pre neoplastic change in the epithelium on which they are painted because pure epidermal grafts of carcinogen treated skin transplanted to other sites did not give rise to tumours whilst numerous tumours appeared on the original treated donor site (Billingham Orr and Woodhouse 1951) moreover the epithelium from which the latter tumours were derived must have arisen by ingrowth from the surrounding untreated epidermis (Orr 1955) Linell (1947) showed that wounding the dermis of animals after treating the skin with methylcholanthrene was followed by an increased tumour response in the scars, but wounds restricted to the epidermis did not increase the incidence of tumours

Epithelium within the dermis may be the origin of the tumours, since Lacassagne and Latarjet (1946) found that repeated applications of methylcholanthrene begun 10 days after the infliction of ultraviolet burns in mice at a time when hair follicles and sebaceous glands had begun to regenerate was followed by tumours in the scar but applications begun on the day after burning when hair follicles had been destroyed did not produce tumours Gillman and Penn (1956) suggested that downgrowths of epithelial spurs from the epidermis may be the source of later malignant epithelium

In summary an abnormal dermal environment of epithelium appears to be necessary for the development of skin carcinoma and cancers developing in old burn scars are examples of this Whether the underlying abnormality is the liberation of growth promoting substances from abnormal or degenerating collagen or the influence of the nervous system or circulating disturbances in the scar as postulated by Murakami (1949) is impossible to say and further work is obviously necessary

Clinical Implications.—The prevention of scars is the ideal at which to aim and although that is not always possible the degree and extent of scarring can be minimized by efficient therapy The rapid natural healing of partial skin loss burns should be encouraged by preventing infection and by the prohibition of local applications such as tannic acid silver nitrate propamidine gentian violet triple dye and other substances which damage or destroy epithelium Such substances delay healing and may even increase the depth of necrosis transforming a partial skin loss burn into a whole skin loss wound and thereby sponsoring the development of granulation tissue and cicatrization

than 50 years The ages of the patients ranged from 19 to 84 years, 80 per cent were more than 40 years of age and 37 per cent were older than 60 years This is because of the long latent period necessary before there is a malignant change

Scar cancer has a preference for male skin, since 70–80 per cent of the cases occurred in males However the preference for male skin may be greater than this indicates because the majority of burned patients are females, particularly those who are burned in childhood The difference may be because the skin of most men, particularly of the hands, is exposed to greater trauma than the skin of women

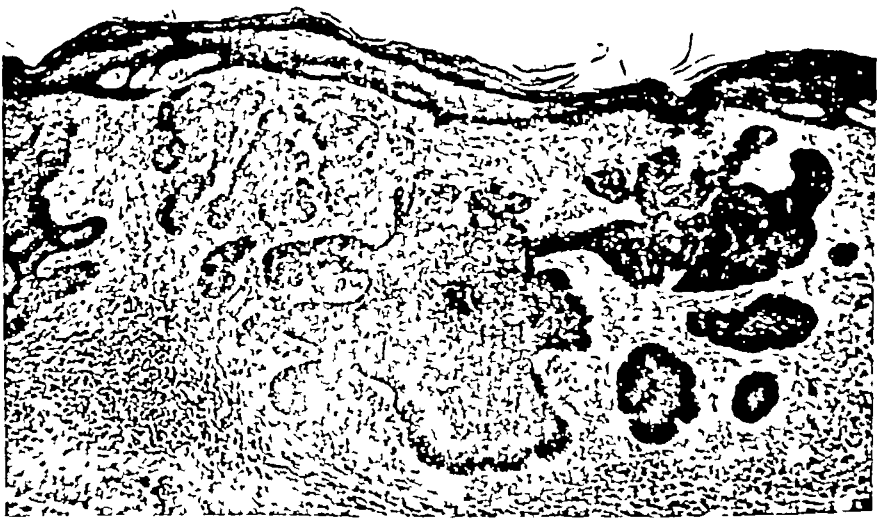


FIG 42 —Basal-cell part of a mixed basal-cell–sweat-duct carcinoma on the site of a burn 15 years previously Patient was an elderly man and had a small ulcer on the back of the hand for 2 years Local excision and grafting, no recurrence 5 years later (Haematoxylin and eosin, × 52)

Chronic irritation —All workers agree that chronic irritation of the scarred skin predisposes to the malignant change Pruritus is a dangerous complication because it leads to scratching The delicate epithelium is easily injured and destroyed repeated injury is important because abrasions, fissures and ulcers form They heal with difficulty because they become infected and because the scar is poorly vascularized and the epidermis is imperfectly nourished In some patients a subsequent burn on the same area or x-irradiation of the chronic ulcer was followed by a malignant change

Dermal-epidermal relationship —The development of cancer in the *scarred* area suggests that the abnormal dermis plays an important role There is evidence that alterations in the dermis are important

occurred in scars years after burning Niedelman's case began as a marble-sized nodule which grew to a large fungating ulcerated cauliflower shaped mass Histologically it appears to have been an undoubted fibrosarcoma and not an anaplastic carcinoma. One of Harkins's cases was possibly an anaplastic carcinoma and the fibrosarcomatous transformation in the other patient may have resulted from x ray therapy to the keloid scars

REFERENCES

Arndt, G (1933) *Beitr klin Chir* 157 305
Billingham, R E., Orr J W., and Woodhouse D L. (1951) *Brit J Cancer* 5, 417
Converse, J M., and Robb-Smith, A H T (1944) *Ann Surg.*, 120, 873
Danzis, M., Friedman, M and Levinson, L J (1938) *Amer J Surg.*, 41 304
Durand, C (1888) *De l'epithelioma pavimenteux primitif des cicatrices* Paris
Geschickter C. F., and Lewis, D (1935) *Amer J Cancer* 25, 630
Gillman, T and Penn, J (1956) *Med Proc S Afr.*, 2, 121 Supple. No 3
— — Bronks, D., and Roux, M (1953–54) *Brit J plast Surg* 6, 153
Glover D M., and Kiehn, C L (1949) *Amer J Surg* 78, 772.
Glucksmann A. (1945). *Brit med Bull* 3 111
— (1951). *Brit J plast Surg* 4 88
Harkins, H. N (1942) *Treatment of Burns* Springfield Thomas.
Hawkins, C. (1825) *Ass Med. Chir* 19 19 (cited by Treves and Pack).
Jacobsson, F (1948) *Acta Radiol* 251
Johnson F M (1926) *Ann. Surg*, 83, 165
Kusano N (1953) *Atomic Bomb Injuries* Tokyo Tsukiji Shokan Co.
Lacassagne, A. and Latarjet R. (1946) *Cancer Res* 6, 183
Levi, J M (1956) Personal communication
Linell, F (1947) *Acta path. microbiol scand* 71 1
Macomber, W B., and Trabue, J C (1951) *Plast reconstr Surg* 7 152.
Marjolin, J N (1828) In *Dictionnaire de Médecine* Vol. 21 p 46. Paris Béchet
Mason, M L (1929) *Arch. Surg* 18, 2107
Mowlem R (1951) *Brit J plast Surg*, 4, 113
Murakami, T (1949) *Rinsho geka* 4, 291
Neve E. F (1923) *Brit med. J* 2, 1255
Niedelman, M L. (1946) *Ann Surg* 123, 311
Orr J W (1955) *Brit J Cancer* 9 623
Shrek, R. (1941) *Arch path* 31 434
Silva, M S (1947) *Rev bras Cancer* 1 67
Taylor G W., Nathanson, I T and Shaw D T (1941) *Ann Surg* 113 268
Treo M (1950). *Riv Infort.*, 37 120.
Treves, N., and Pack, G T (1930) *Surg Gynec Obstet* 51 749
Vargas, L (1943) *Johns Hopk Hosp Bull* 73, 23

Early excision and skin grafting of whole skin-loss burns is most important. By preventing hypertrophic granulations skin grafting greatly reduces the amount of scar tissue, and by replacing skin surface it prevents or greatly reduces contracture. The complete correction of skin shortage will prevent cracks and fissures and this is probably the surgeon's greatest contribution to reducing the risk of malignant change. Skin grafting is particularly important in children, because in later life their scars are old and are probably more liable to malignant change. The nature of the grafts is important. Pinch grafts do not prevent scarring and subsequent contractures are potential sites for carcinoma. Two cases of skin cancer developing in burn scars originally treated with pinch grafts were reported by Danzis, Friedman and Levinson (1938). Perhaps grafts of the full thickness of the skin should be used if possible unless the extent of the burn makes it necessary to employ split-skin grafts. Treves and Pack (1930) point out that the latter do not produce normal skin, their surfaces remain dry because sweat and sebaceous glands are few or absent and therefore they are subject to similar carcinogenic influences as ordinary scars. Only a long term follow-up of grafted patients will determine how much truth there is in this.

Degenerative changes in scars including simple ulceration should be regarded as ominous signs, and radical excision and skin grafting are indicated. Macomber and Trabue (1951) warned that any chronic ulcer in a burn scar should be considered to be malignant until proven otherwise.

KANGRI AND KAIRO BURN CANCER

The Kangri of the Kashmiris is an earthenware pot filled with charcoal and suspended in a wicker frame. It is worn mainly by men under the garments against the lower abdomen and inner sides of the thighs as a source of heat. The Japanese Kairo is a curved metal box also filled with charcoal, it is used as a source of heat by women and worn under the kimono against the abdomen. Continued use of these heating instruments produces *erythema ab igne*, chronic dermatitis and burn scars. Squamous-cell carcinoma may develop on the skin of the inner parts of the thighs and lower abdomen among the Kashmiris and on the front of the abdomen among the Japanese. An account of Kangri cancer is given by Neve (1923), who found it quite common.

SARCOMA

This is a very rare complication of burns. Two possible cases were reported by Harkins (1942) and one by Niedelman (1946). All three

to the burn, that is contamination may be followed by their multiplication and the growth of tiny colonies Large numbers of potentially pathogenic microbes like *Str pyogenes* or *Ps pyocyanea* are likely to produce clinical effects The combination of contamination (particularly colonization) and clinical effects means infection

The results of infection may be classified as (1) local (2) invasive and (3) toxic

Local changes —Pain a spreading cellulitis a prolonged inflammatory oedema or a local spread of inflammation may result Sometimes the effects are obvious but more often they are apparently silent and difficult to distinguish clinically from the normal effects of acute burn inflammation and the later sloughing and granulation tissue formation Adverse changes may be manifest only by a delayed healing, a failure of skin grafts to take or by excessive scarring of the skin Interference by bacterial infection in the healing of partial skin loss burns from which haemolytic streptococci and staphylococci were isolated was noted histologically by Gordon and his colleagues (1946) Apposition of newly spread epithelium over the dermis was sometimes focally unsuccessful and the epithelial cells were found lying detached in or on a purulent exudate

Invasive complications —*Septicaemia* and *bronchopneumonia* from bacteria present in the burn are relatively common causes of death in extensively burned patients Occasionally pyaemia meningitis, bacterial endocarditis or pyelonephritis is diagnosed or is found at autopsy The frequency of septicaemia has been stressed by Liedberg, Reiss and Artz (1954) who attributed 15 out of 35 deaths after burning to this cause The clinical state of high fever tachycardia polypnoea and associated effects attributed to toxaemia may often be due to septicaemia The organisms incriminated include *Str pyogenes Staph aureus Ps pyocyanea* and at times *Proteus Bact coli* and other coliform bacilli and occasionally *Cl welchii* It should be noted that special technical precautions are necessary to avoid contamination of blood cultures from patients with heavily colonized burns Moreover a burned patient dying of causes unrelated to infection (such as renal failure) may develop a terminal bacteraemic invasion Mixed cultures are difficult to interpret particularly when different bacteria are isolated on different occasions

Toxaemia —Specific toxaemic effects are burn scarlatina and rarely tetanus Non specific bacterial toxaemia may also be important and may give rise not only to malaise a continued pyrexia and tachycardia but may also contribute to the loss of flesh and anaemia

CHAPTER 6

THE ROLE OF INFECTION IN BURNS

UNTIL recently surgeons regarded clinical infection of whole skin-loss burns as inevitable and the importance of bacterial contamination was not generally recognized The papers of Aldrich (1933), Dunbar (1934) and Cruickshank (1935) awakened an interest in the bacterial flora of burns and stressed the importance of infection with haemolytic streptococci, Aldrich claiming that the so-called toxaemic clinical state was the result of infection

It is now recognized that the problem of infection in burns is the problem of wound infection writ large and a burn may be regarded as an easily contaminated open wound

THE BACTERIAL FLORA OF BURNS

There are wide variations in the number and variety of bacteria which may be isolated Fresh burns are often sterile, but even when special precautions are taken to prevent contamination some bacteria are soon added It is not generally appreciated how rapidly this occurs (*see* Chapter 7) A full list of the microbes which may be found would constitute a veritable bacterial zoo, usually more than one species is isolated from a single area and frequently the bacterial flora is mixed The most important pathogenic or facultatively-pathogenic bacteria are *Streptococcus pyogenes* (Lancefield's Group A haemolytic streptococci), *Pseudomonas pyocyanea* and *Staphylococcus aureus* (coagulase-positive staphylococci), *Proteus*, *Bacterium coli* and various other coliform and paracolon bacilli are probably important at times Organisms which are usually of little significance include various other Gram-positive cocci such as micrococci and coagulase-negative staphylococci, diphtheroid bacilli, aerobic sporing bacilli, members of the *Neisseria* group (Gram-negative cocci) and many other streptococci On the other hand heavy colonization of whole skin-loss burns with these saprophytic bacteria is not necessarily unimportant since the very abundance of bacteria might on occasion have adverse local and systemic effects *Clostridium welchii* and other anaerobic sporing bacilli may also be isolated

Contamination and infection The distinction between bacterial contamination and infection is often difficult Addition of bacteria

to the burn, that is *contamination* may be followed by their multiplication and the growth of tiny colonies Large numbers of potentially pathogenic microbes like *Str pyogenes* or *Ps pyocyanea* are likely to produce clinical effects The combination of contamination (particularly colonization) and clinical effects means infection

The results of infection may be classified as (1) local (2) invasive and (3) toxic.

Local changes—Pain a spreading cellulitis, a prolonged inflammatory oedema, or a local spread of inflammation may result Sometimes the effects are obvious but more often they are apparently silent and difficult to distinguish clinically from the normal effects of acute burn inflammation and the later sloughing and granulation tissue formation Adverse changes may be manifest only by a delayed healing, a failure of skin grafts to take or by excessive scarring of the skin Interference by bacterial infection in the healing of partial skin loss burns from which haemolytic streptococci and staphylococci were isolated was noted histologically by Gordon and his colleagues (1946) Apposition of newly spread epithelium over the dermis was sometimes focally unsuccessful and the epithelial cells were found lying detached in or on a purulent exudate

Invasive complications—*Septicaemia* and *bronchopneumonia* from bacteria present in the burn are relatively common causes of death in extensively burned patients. Occasionally pyaemia meningitis, bacterial endocarditis or pyelonephritis is diagnosed or is found at autopsy The frequency of septicaemia has been stressed by Liedberg Reiss and Artz (1954) who attributed 15 out of 35 deaths after burning to this cause The clinical state of high fever tachycardia, polypnoea and associated effects attributed to toxaemia may often be due to septicaemia The organisms incriminated include *Str pyogenes Staph aureus Ps pyocyanea* and at times *Proteus Bact coli* and other coliform bacilli and occasionally *Cl welchii* It should be noted that special technical precautions are necessary to avoid contamination of blood cultures from patients with heavily colonized burns Moreover a burned patient dying of causes unrelated to infection (such as renal failure) may develop a terminal bacteraemic invasion Mixed cultures are difficult to interpret particularly when different bacteria are isolated on different occasions

Toxaemia—Specific toxaemic effects are burn scarlatina and rarely tetanus Non specific bacterial toxaemia may also be important and may give rise not only to malaise a continued pyrexia and tachycardia but may also contribute to the loss of flesh and anaemia.

Such a toxaemia may really be an undiagnosed septicaemia There is now no reasonable doubt that one of the main causes of acute toxaemia in burns are bacteria and their products and not the unspecified toxic substances released from burned skin (Chapter 12)

FACTORS INFLUENCING THE BACTERIAL FLORA

The bacteria isolated from a burn may not only vary from patient to patient but may also alter with time in the same burn The importance of therapy and the relative roles of self-infection and cross-infection are considered in the next chapter The other factors influencing the bacterial flora are (1) the depth of burning, with which are associated the rapidity of healing and tissue changes in the burned area, (2) the site of burning and (3) possibly mutual antagonism among bacteria

Depth of burning.—Superficial burns heal rapidly and the opportunities for infection are limited in time Deep burns heal slowly or fail to heal and the opportunities for infection are more prolonged In addition the formation of a necrotic slough appears to have an influence on the bacterial flora which frequently becomes more abundant and varied

Colebrook and his colleagues (1945) broadly classified the bacterial findings according to the time after burning and the nature of the changes in the burned skin as shown below

(1) The coccal infections of the first week, mainly by haemolytic streptococci and staphylococci

(2) The abundant mixed coccal and bacillary infection of deep burns in the second to the fourth week found whilst necrotic skin was separating The flora often consisted of diphtheroid bacilli, *Ps pyocyanea*, *Proteus* and various coliform bacilli in addition to staphylococci and streptococci

(3) The later mainly coccal infections of the granulating period Healthy granulation tissue was usually associated with a reduced bacterial flora *Staph aureus* was the main organism, but haemolytic streptococci were sometimes present Unhealthy pale, oedematous granulation tissue with abundant exudation was commonly associated with a heavier mixed flora containing either *Ps pyocyanea*, *Str pyogenes*, *Proteus* or coliform bacilli or various combinations of these bacteria, but the abnormal granulation tissue may have been the result rather than the cause of the different flora

Altemeier (1951) agreed that the bacterial flora increased and altered when the skin sloughed and he believed that this was because dead tissue was readily invaded by bacteria and supported their growth well

Site of burning.—The anatomical location of a burn may influence bacterial contamination in two ways Firstly the normal flora near the burn may be expected to contaminate it Langohr Owen and Cope (1947) found that burns of the lower extremity were contaminated with faecal organisms such as *Cl welchii* and enterococci more frequently than burns elsewhere and Korlof (1956) noted the association of *Proteus* with burns in the anal region Secondly the opportunities of contamination are reduced when the burn can be perfectly covered by a dressing and this depends on the anatomical area burned. Lowbury and Fox (1954) isolated *Ps pyocyanea* much less frequently from burned hands and feet which could be adequately covered by bandaging than from the trunk, face or scalp which were difficult to keep efficiently covered

Mutual antagonism among bacteria.—Analysing the mixed bacterial flora of burns Korlof (1956) concluded that faecal organisms (coliform bacilli enterococci, *Ps pyocyanea* and *Proteus*) were antagonistic to staphylococci. He found that when staphylococci were abundant the others were sparse or absent and vice versa On the other hand, he isolated haemolytic and viridans streptococci irrespective of the other bacteria present Other workers have not reported this mutual antagonism.

THE ROLE OF CERTAIN BACTERIA

Streptococcus pyogenes.—This organism is the most feared of all It can increase the local damage to even superficial burns delay healing, prevent skin grafts from taking and is sometimes responsible for a spreading cellulitis or septicaemia which may endanger life At autopsy Cruickshank (1935) isolated haemolytic streptococci from the spleens of 3 out of 6 fatally burned patients who had harboured this organism in their burns and from small endocardial vegetations in one of them. Colebrook and his colleagues (1945) compared the mean daily temperatures of a group of patients whose burns were treated locally with an antistreptococcal cream (containing a sulphonamide or penicillin) with the mean temperature of other patients not so treated Both groups were equally pyrexial after burning (reaction to injury) but the temperature of those receiving chemotherapy fell to normal in 4–6 days whereas the mean temperature of the others took 12 days to return to normal

Severe local inflammatory changes in burns and other wounds colonized by haemolytic streptococci have been noted by various workers, including Meleney (1943 1945) Colebrook and his colleagues (1945) Jackson Lowbury and Topley (1951a) and Korlof

(1956) In Colebrook's series the burns of 20 of the 84 patients with haemolytic streptococci became purulent but streptococcal contamination of the majority was without local or general signs This may have been the result of the sulphanilamide cream applied to the burns which may have reduced the numbers of streptococci or possibly their "aggressiveness", but silent infections may also occur in untreated burns

An association of silent or overt streptococcal infection with delayed healing was noted by Bodenham (1943) and with frequent failure of skin grafts by Clarkson and Lawrie (1946) This suggested that *Str pyogenes* was responsible The role of this organism in graft failure was studied by Lowbury and Cason (1954) One series of whole skin-loss burns was cleared of streptococci by local aureomycin therapy and skin-grafted, other burns containing *Str pyogenes* were skin-grafted without aureomycin therapy Graft failure occurred in 25 per cent of the former group and in 89 per cent of the latter group This confirmed a previous analysis which indicated that the presence of *Str pyogenes* doubled the rate of graft failure (Jackson, Lowbury and Topley, 1951a) Similar results were found by Liedberg and his colleagues (1954) using a locally applied chloramphenicol ointment or a Furacin dressing as an antistreptococcal agent

The mechanism of the graft failure is uncertain but streptococcal fibrinolysin which could digest the fibrin clot under the split-skin graft is a possible cause

Burn scarlatina —Only a minority of patients whose burns harbour haemolytic streptococci develop a generalized scarlatiniform rash Only 2 out of 112 such patients were reported by Jackson, Lowbury and Topley (1951a), but some workers report a higher frequency of rashes, for example, 14 cases out of 90 patients were reported by Deuretsbacher and Kellner (1948) in Vienna Like the exanthema of scarlet fever the rash spares the face and an intracutaneous injection of Dick antitoxin is followed by circumscribed disappearance of the erythema Cruickshank (1935) reported 10 cases and noted that the rash developed at varying times after admission to hospital He believed that the burn rather than the throats of the patients was the primary focus of the infection Presumably the specific erythrogenic toxin is produced in the burned skin and is absorbed directly into the circulation Burn scarlatina was studied clinically by Varshavskii (1947), who concluded that it occurs as a rule only in children, that it does not depend either on the character or the location of the burn, and that complications are less frequent than in ordinary scarlatina

He isolated haemolytic streptococci from the burn in 28 per cent of cases and from the pharynx and nose in 62 5 per cent

Staphylococcus aureus.—This is the most frequent contaminant of all wounds, including burns De Waal (1943) cultured it from more than 50 per cent of burns, Varshavskii (1947) and Colebrook Duncan and Ross (1948) reported that 60–70 per cent of severely burned patients acquired this organism during their stay in hospital, and an even higher rate of contamination was found by Langohr Owen and Cope (1947) Kashkin and his colleagues (1949) Altemeier (1951) Lowbury Topley and Hood (1952) and Korlof (1956) Staphylococci continue to be prevalent in spite of the use of penicillin aureomycin and other antibiotics due to the emergence and spread of resistant strains (*vide infra*)

The pathogenic role of this organism in boils, carbuncles and other local conditions is well known and also its invasive potentiality in osteomyelitis septicaemia and other conditions. In burned patients it may cause septicaemia or pyaemia and be associated with bronchopulmonary infections (Clarkson and Lawrie 1946)

Like other bacteria its local significance in a burn is difficult to assess. Sen (1948) reported 21 cases of sepsis among 39 patients with *Staph aureus* in their burns and noted that this sepsis delayed healing. Broadly speaking the healing of partial skin loss burns is rarely affected Langohr Owen and Cope (1947) described a local proteolytic reaction in the burns of 9 patients from whom this organism and *Proteus* were isolated When the skin disappeared or the grafts failed the yellow subcutaneous tissue was exposed without deeper inflammation or formation of granulation tissue Eventual healing of the burns coincided with a rise in the specific anti staphylococcal agglutinin content of the patient s serum From these and other patients they concluded that the immune reaction of the body was important in staphylococcal infection

On the other hand Colebrook and his co-workers considered that staphylococci produced infrequent and relatively slight local effects (Colebrook and his colleagues, 1945 Colebrook Duncan and Ross, 1948) and this is supported by Korlof (1956) In the early stages after burning, slight suppuration with little or no pyrexia might be found but only very occasionally was there a profuse suppuration of the burn

The deleterious influence of staphylococci on skin grafting is less than that of *Str pyogenes* but some workers believe that this agent might have an adverse effect The report of Lowbury (1954) suggests that staphylococci are also capable of preventing the take of grafts and that elimination of this organism increases the number of

(1956) In Colebrook's series the burns of 20 of the 84 patients with haemolytic streptococci became purulent but streptococcal contamination of the majority was without local or general signs This may have been the result of the sulphanilamide cream applied to the burns which may have reduced the numbers of streptococci or possibly their "aggressiveness", but silent infections may also occur in untreated burns

An association of silent or overt streptococcal infection with delayed healing was noted by Bodenham (1943) and with frequent failure of skin grafts by Clarkson and Lawrie (1946) This suggested that *Str pyogenes* was responsible The role of this organism in graft failure was studied by Lowbury and Cason (1954) One series of whole skin-loss burns was cleared of streptococci by local aureomycin therapy and skin-grafted other burns containing *Str pyogenes* were skin-grafted without aureomycin therapy Graft failure occurred in 25 per cent of the former group and in 89 per cent of the latter group This confirmed a previous analysis which indicated that the presence of *Str pyogenes* doubled the rate of graft failure (Jackson, Lowbury and Topley, 1951a) Similar results were found by Liedberg and his colleagues (1954) using a locally applied chloramphenicol ointment or a Furacin dressing as an antistreptococcal agent

The mechanism of the graft failure is uncertain but streptococcal fibrinolysin which could digest the fibrin clot under the split-skin graft is a possible cause

Burn scarlatina —Only a minority of patients whose burns harbour haemolytic streptococci develop a generalized scarlatiniform rash Only 2 out of 112 such patients were reported by Jackson, Lowbury and Topley (1951a), but some workers report a higher frequency of rashes, for example, 14 cases out of 90 patients were reported by Deuretsbacher and Kellner (1948) in Vienna Like the exanthema of scarlet fever the rash spares the face and an intracutaneous injection of Dick antitoxin is followed by circumscribed disappearance of the erythema Cruickshank (1935) reported 10 cases and noted that the rash developed at varying times after admission to hospital He believed that the burn rather than the throats of the patients was the primary focus of the infection Presumably the specific erythrogenic toxin is produced in the burned skin and is absorbed directly into the circulation Burn scarlatina was studied clinically by Varshavskii (1947), who concluded that it occurs as a rule only in children, that it does not depend either on the character or the location of the burn, and that complications are less frequent than in ordinary scarlatina

by Jackson Lowbury and Topley (1951b) Liedberg Reiss and Artz (1954) and others The complications listed have been septicaemia and pneumonia and to these may be added bacterial endocarditis pyaemia and pyelonephritis

Proteus and other Gram-negative coliform bacilli.—*Proteus* and other coliform bacilli such as *Bact coli* and paracolon bacilli are relatively common invaders particularly during the sloughing and granulating period of burns They are also more commonly isolated from burns near the gluteal area Colebrook Duncan and Ross (1948) isolated *Proteus* from 6 out of 734 burns (0 8 per cent) on admission and from 89 (12 per cent) during the course of their stay in hospital Korlof (1956) reported added contamination with this organism in 22 per cent of cases and Altemeier (1951) found Gram negative intestinal bacilli including *Proteus* in 52–84 per cent of burns The individual roles of *Proteus* and these other bacteria are difficult to determine because they are often found together and other organisms like *Ps pyocyanea* various streptococci and staphylococci may also be found. Colebrook and his colleagues thought that *Proteus* did little harm but Korlof (1956) Altemeier (1951) and others considered that heavy colonization might have adverse local effects producing pyrexia and affecting the general condition of the patient Skin graft failure has been attributed to *Proteus* and *Proteus* bacteraemia or septicaemia has occurred As had already been mentioned, Jackson Lowbury and Topley (1951b) considered that polymyxin sensitive coliform bacilli play a part in delayed healing and graft failure

Clostridium tetani and tetanus.—Few workers have reported on the incidence of *Cl tetani* in burns but it is probably uncommon Lowbury (1956) rarely saw terminal sporing bacilli in stained preparations from cooked meat broth cultures In fresh burns Hoge (1945) found *Cl tetani* in 4–5 per cent of cases and Altemeier (1951) reported it in 3 per cent.

Tetanus is a rare complication in most countries whether or not the patient receives an injection of antitoxin or toxoid During the last eight years only one case occurred among over 3 000 in-patients in the Burns Unit in Birmingham As a consequence neither toxoid nor antitoxin is given as a routine prophylactic because the rarity of tetanus does not warrant the risk of unfavourable reactions Two cases were reported by Mazzini (1947) and single cases by Perdrup (1949) and Holmdahl and Thoren (1954) Perdrup s case is of special interest because fatal tetanus developed in spite of giving antitoxin toxoid and penicillin on admission

successful takes The graft failure potentiality might be related to staphylococcal necrotoxin or fibrinolysin, but a complete explanation would have to take into account the infrequent harmful effect of staphylococcal contamination

Pseudomonas pyocyanea.—At times this organism is also a common colonizer of burns, although it is found less commonly than staphylococci Its incidence varies considerably from time to time The clinical effects of local infection are less obvious than those due to *Str pyogenes* but more definite than those due to *Staph aureus* Sometimes colonization is associated with local inflammation and profuse exudation or "toxaemic" pyrexia but more often no obvious signs are found When apparently silent its presence has been incriminated with delayed healing and failure of skin grafting (Bodenham, 1943, Colebrook, Duncan and Butterfield, 1947) The pathogenic role of this organism in burns was studied by Jackson, Lowbury and Topley (1951b) Two groups of patients were compared in a prophylactic clinical trial the burns of one group were treated locally both with penicillin and polymyxin (to which *Ps pyocyanea* and certain coliform bacilli are sensitive) whilst the burns of the other group were treated with local penicillin The addition of polymyxin produced a considerable reduction in the rate of contamination by *Ps pyocyanea* and coliform bacilli, a significant reduction in the incidence of graft failure and healing time of whole skin-loss burns, and a slight reduction in the incidence of anaemia, pyrexia and death Graft failure was attributed to the blue pigment pyocyanin which frequently stains the exudate from burns colonized by *Ps pyocyanea* (Cruickshank and Lowbury, 1953) Pyocyanin was proved to be epidermotoxic by adding the pigment to cultures of human skin *in vitro*, its toxic concentrations were similar to the concentrations extractable from stained dressings covering burns

An immune response to colonization by *Ps pyocyanea* was found by Fox and Lowbury (1953) The blood sera from one-third of 39 patients who had acquired *Ps pyocyanea* in their burns had a high agglutinin titre (more than 1 in 320) against this organism, whilst similar titres were found in only 1 out of 23 patients without *Ps pyocyanea* Moreover there was evidence that the titre increased with the passage of time, and was also higher in the patients with the larger burns Particularly high titres were found in patients with a local or generalized clinical infection in which *Ps pyocyanea* was the dominant organism

Burned patients who have died with evidence of systemic complications resulting from invasion of *Ps pyocyanea* have been described

by Jackson, Lowbury and Topley (1951b) Liedberg, Reiss and Artz (1954) and others. The complications listed have been septicaemia and pneumonia and to these may be added bacterial endocarditis, pyaemia and pyelonephritis.

Proteus and other Gram-negative coliform bacilli —*Proteus* and other coliform bacilli such as *Bact coli* and paracolon bacilli are relatively common invaders particularly during the sloughing and granulating period of burns They are also more commonly isolated from burns near the gluteal area. Colebrook Duncan and Ross (1948) isolated *Proteus* from 6 out of 734 burns (0 8 per cent) on admission and from 89 (12 per cent) during the course of their stay in hospital Korlof (1956) reported added contamination with this organism in 22 per cent of cases and Altemeier (1951) found Gram negative intestinal bacilli including *Proteus* in 52–84 per cent of burns. The individual roles of *Proteus* and these other bacteria are difficult to determine because they are often found together and other organisms like *Ps pyocyanea* various streptococci and staphylococci may also be found. Colebrook and his colleagues thought that *Proteus* did little harm, but Korlof (1956) Altemeier (1951) and others considered that heavy colonization might have adverse local effects, producing pyrexia and affecting the general condition of the patient Skin graft failure has been attributed to *Proteus* and *Proteus* bacteraemia or septicaemia has occurred. As had already been mentioned Jackson Lowbury and Topley (1951b) considered that polymyxin sensitive coliform bacilli play a part in delayed healing and graft failure

Clostridium tetani and tetanus.—Few workers have reported on the incidence of *Cl tetani* in burns but it is probably uncommon Lowbury (1956) rarely saw terminal sporing bacilli in stained preparations from cooked meat broth cultures. In fresh burns Hoge (1945) found *Cl tetani* in 4–5 per cent of cases and Altemeier (1951) reported it in 3 per cent.

Tetanus is a rare complication in most countries whether or not the patient receives an injection of antitoxin or toxoid During the last eight years only one case occurred among over 3 000 in patients in the Burns Unit in Birmingham As a consequence neither toxoid nor antitoxin is given as a routine prophylactic because the rarity of tetanus does not warrant the risk of unfavourable reactions Two cases were reported by Mazzini (1947) and single cases by Perdrup (1949) and Holmdahl and Thoren (1954) Perdrup s case is of special interest because fatal tetanus developed in spite of giving antitoxin toxoid and penicillin on admission.

Other bacteria.—Other bacteria are occasionally involved *Clostridium welchii and other anaerobic sporing bacilli*—Altemeier (1951) reported a very high frequency (70 per cent) of *Cl welchii* in fresh burns and an incidence of about 6 per cent in burns during the sloughing or granulating period Lowbury (1956) finds this organism at one time or another on the burns of about 20 per cent of patients The pathogenic role, if any, of clostridia in burned skin is not defined Occasionally it has been isolated by blood culture but even then its significance is uncertain

Other streptococci—Streptococci of Lancefield's groups C, G and D have been reported by various workers They are usually infrequent, but Liedberg and his colleagues (1954) reported a relatively high incidence of Group D strains (enterococci) Other streptococci including non-groupable haemolytic strains, various non-haemolytic and viridans streptococci and anaerobic strains may also be isolated (Kashkin and his colleagues, 1949) Clinical trials by Jackson, Lowbury and Topley (1951a) and Liedberg and his colleagues (1954) did not indicate that streptococci of Groups C, D or G contributed to graft failure

Diphtheroid bacilli—These are commonly found in burns and wounds and are generally believed to be saprophytic On one occasion the author isolated a toxigenic strain of *Corynebacterium diphtheriae* from the burned skin of a child but the patient showed no evidence of clinical diphtheria Herrman and Putz (1943) studied 80 diphtheroid strains from burns of which 65 biochemically resembled *C diphtheriae* but the organisms were non-pathogenic

Bacteroides and other non-sporing bacteria were isolated from 10 per cent of recent burns by Altemeier (1951)

ANTIBIOTIC-RESISTANT BACTERIA IN BURNS

The discovery of chemotherapeutic agents has greatly advanced the treatment of infections but the early hope that they would greatly ease the problem of wound infection *within hospitals* has not been fulfilled Paradoxically it was the extensive and at first the successful use of the antibiotics which was responsible for this The major problem now is *Staph aureus*, many strains of which have become resistant to antibiotics and endemic in hospitals When antibiotic-resistant strains emerged they spread by cross-infection, and the continued use of the antibiotic ensured that the incidence of infection by sensitive strains declined and the incidence by resistant strains increased

Emergence of resistant bacteria—adaptation and selection.—Two theories have been advanced to explain the emergence of resistant strains, namely (1) adaptation and selection and (2) selection without adaptation Resistance through adaptation is an acquired resistance It implies firstly that a specific (probably metabolic) change has been produced which allows the now altered organism to grow and reproduce in the presence of the antibiotic secondly the change is permanent and the acquired power of resistance is transmissible to subsequent generations Evidence of this has been presented by Barber (1953) and others A small proportion of the flora acquires resistance but in the presence of the antibiotic the sensitive bacteria are restrained and the resistant cells selectively grow outnumber and finally replace the sensitive organisms Resistance through selection *without adaptation* (Demerec 1945) means that small numbers of resistant bacteria were present before the antibiotic was used or that they arose through chance mutation independent of the antibiotic The antibiotic merely selects the resistant organisms at the expense of the sensitive ones. This implies, for example that certain strains of *Staph aureus* contained small numbers of organisms resistant to penicillin streptomycin aureomycin chloromycetin or erythromycin and so on even before the discovery of these agents, and that present cultures contain a few bacteria resistant to antibiotics which have not been discovered.

Antibiotic resistance of common wound pathogens.—Resistance to an antibiotic may be natural as well as acquired and different species of bacteria vary in their natural susceptibility and their power to acquire resistance

Staphylococcus aureus —The central problem is the ease with which certain strains of this ubiquitous bacterium acquire resistance to penicillin, aureomycin terramycin chloramphenicol streptomycin erythromycin and other agents Penicillin resistance acquired *in vivo* is unique in that the organism acquires the power to destroy penicil lin that is penicillinase activity Resistance to other antibiotics is not accompanied by the power to destroy the antibiotic Phage typing has shown that certain strains acquire penicillinase activity more readily than others mainly strains of the 6/47 group (Williams, Rippon and Dowsett 1953) and that resistance to aureomycin chloromycetin terramycin and erythromycin occurs almost entirely among the penicillinase producing strains

Colebrook found that penicillin cream in burns was initially successful not only against *Str pyogenes* but also against *Staph aureus* (Clarke and his colleagues 1943) but a few years later in

Birmingham he reported that the early success could not be maintained and that penicillin-resistant strains of *Staph aureus* were being frequently isolated (Colebrook, Duncan and Ross, 1948) A subsequent prophylactic clinical trial of penicillin cream was ineffective for staphylococci and 70 per cent of the strains were penicillin-resistant (Jackson, Lowbury and Topley, 1951a) The sequel of early success and ultimate failure recurred when aureomycin was introduced (Lowbury, Topley and Hood, 1952) Success was due to the initial susceptibility of the staphylococci to aureomycin, and failure was due to the emergence of aureomycin-resistant strains which spread through cross-infection Subsequently the introduction of erythromycin was followed by the isolation of erythromycin-resistant staphylococci from burned patients (Lowbury and Cason, 1954)

Similar experiences have been reported from many countries (Langohr, Owen and Cope, 1947, Altemeier, 1951, Korlof, 1956)

However, the use of some of the newer agents such as neomycin, novobiocin, vancomycin and chlorhexidine (Hibitane), preferably in combination with others, apparently does not result in the emergence of resistant strains and offers hope for the control of this organism

Streptococcus pyogenes—Fortunately this organism differs from *Staph aureus* in that resistance to penicillin is almost unknown, but unfortunately penicillin therapy is seriously limited when penicillinase-producing staphylococci are also present (Cruickshank, Squire and Topley, 1948) Failure is attributed to staphylococcal penicillinase which presumably destroys the locally applied penicillin

Local sulphonamide therapy was at first successful against *Str pyogenes* but continued use was followed by the emergence of sulphonamide-resistant strains (Colebrook and his colleagues, 1945) More recently aureomycin therapy in burns has been followed by the emergence of tetracycline-resistant strains of *Str pyogenes* (Lowbury and Hurst, 1956) Most of these differ from the majority of Group A streptococci in that they are anaerobic when first isolated and produce little or no haemolysis on blood agar plates This makes them more difficult to isolate and to identify On subculture they revert to aerobic growth and regain the power to produce haemolysis but they retain their tetracycline-resistance

Pseudomonas pyocyanea—All strains of this organism appear to be very sensitive to the polymyxins, and local therapy with polymyxin E in burns has fortunately not been followed by the emergence of resistant strains (Jackson, Lowbury and Topley, 1951b) The resistance of *Ps pyocyanea* to other antibiotics is high

Proteus —Strains of this group of organisms are naturally insensitive to most antibiotics including polymyxin Many strains are initially sensitive or moderately susceptible to streptomycin and chloram phenicol but rapidly acquire resistance *in vitro* and *in vivo* The development of an antibiotic to which this organism is not and does not become resistant is another challenge to pharmacology

REFERENCES

Aldrich, R. H (1933) *New Engl. J Med.*, 208, 299
Altemeier W A. (1951) In *Symposium on Burns* p 132. Washington National Research Council.
Barber M (1953) *J gen. Microbiol* 8, 111
Bodenham, D C (1943) *Lancet*, 2, 725
Clark, A. M., Colebrook, L. Gibson, T., and Thomson, M (1943) *Lancet* 1 605
Clarkson, P., and Lawrie, R S (1946). *Brit J Surg* 33, 311
Colebrook, L. Duncan, J M and Butterfield, W J H (1947) *Lancet* 1 321
— — and Ross, N P D (1948) *Lancet* 1 893
— Clark, A. M Gibson, T and Todd, J P (1945) In *Studies of Burns and Scalds* M R.C. Special Report Series, No 249, Part II
Cruickshank, C. N D and Lowbury E. J L. (1953) *Brit J exp Path* 34, 583
— Squire J R. and Topley E. (1948) *Lancet* 2, 989
Cruickshank, R. (1935) *J Path. Bact.*, 41 367
Demerec, M (1945) *Proc nat Acad Sci Wash* 31 16.
Deuretsbacher H and Kellner, H (1948) *Klin Med.*, 3, 730
Dunbar, J (1934). *Glasgow med. J* 122, 239
Fox, J E. and Lowbury E. J L. (1953) *J Path Bact* 65, 519
Gordon, J., Hall R A., Heggie, R. M and Horne, E. A (1946) *J Path Bact* 58, 51
Herrman W and Pütz, T (1943) *Dtsch med Wschr* 69 744
Hoge W G (1945). *Northwest Univ Bull* 19 111
Holmdahl M H., and Thoren L. (1954) *Acta chir scand* 107 335 (Quoted by Korlof 1956)
Jackson, D McG Lowbury E. J L. and Topley E. (1951a) *Lancet* 2, 705
— — — (1951b). *Ibid.* 2, 137
Kashkin P N Kashkina E. G Mints, B M., and Neelova N S (1949) *Khirurgia* No 4 13
Korlof B (1956). *Acta chir scand.* Suppl., 209
Langohr J L. Owen C R. and Cope O (1947) *Ann Surg* 125, 452.
Liedberg, N C F Kuhn, L. R. Barnes, B A. Reiss, E., and Armspacher W A. (1954) *Surg Gynec Obstet.*, 98, 693
— Reiss, E. and Artz, C P (1954) *Ibid* 99 151
Lowbury E. J L. (1954) *Proc R Soc Med.*, 47 231
— (1956) Personal communication.
— and Cason J S (1954) *Brit med J* 2, 914
— and Fox, J (1954). *J Hygiene* 52, 403
— and Hurst L. (1956). *J clin Path* 9 59
— Topley, E. and Hood, A M (1952) *Lancet* 1 1036
Mazzini, O F (1947) *Bol Acad argent Cirug* 31 199
Meleney F L (1943) *Ann Surg* 118, 171
— (1945) *Surg Gynec Obstet* 80 263
Perdrup A. (1949) *Acta chir scand.*, 97 495
Sen, P K. (1948). *Indian med J* 10, 154
Varshavsku, A B (1947) *Sovet Med* 5 19
Waal H L. de (1943) *Edinb med J.*, 50, 577
Williams, R E. O Rippon J E. and Dowsett, L. M (1953) *Lancet* 1 510

CHAPTER 7

THE EPIDEMIOLOGY AND CONTROL OF INFECTION

DURING the first 30 or 40 years of this century few doctors concerned with burns attempted to prevent bacterial contamination although many recognized the results of infection Burned patients continued to be nursed and dressed in general surgical or even dermatological wards, where cross-infection was frequent Dunbar (1934) notes however that Lister's work influenced the treatment of burns in the Glasgow Royal Infirmary, where local antiseptic treatment with carbolic oil was introduced in 1869 Apparently the next attempt to control infection was that by Aldrich (1933), who found infection by streptococci to be very common and painted the burns with gentian violet and other chemotherapeutic dyes The first epidemiological study was that of Cruickshank (1935), who isolated haemolytic streptococci from the dust of burns wards and related this to the high rate of streptococcal infection

A major epidemiological study combined with a campaign against infection was launched by Colebrook in 1942 in the Burns Unit in Glasgow and later in Birmingham The discovery of the sulphonamides and penicillin had opened the door of chemotherapy, and Colebrook and his colleagues used these agents locally to control infection of burned skin This was part of a multiple attack against bacterial contamination based on the prevention of contact and airborne contamination and the elimination of bacterial reservoirs

EPIDEMIOLOGY

EARLY CONTAMINATION

The act of burning or scalding sterilizes the skin surface although it is possible for organisms deeply placed, for example in hair follicles, to survive Most burns swabbed within an hour or two of injury are sterile (Colebrook and his colleagues, 1945) and bacteria cultured from a burned surface have probably been added after burning The frequency of haemolytic streptococci in the burns of 516 patients arriving at hospital at different times after injury was

investigated by Colebrook Gibson and Todd (1945) in Glasgow This organism is not a normal skin microbe and is carried in the noses or throats of not more than 5 per cent of people Haemolytic streptococci were isolated from 4 per cent of burns arriving within 12 hours of injury from 23 per cent arriving between 12 and 24 hours and from 42 per cent arriving after this Therefore the patients could not have been responsible for contaminating most of these burns

First aid therapy—Bacteria may be added by well meaning friends, relatives and attendants The relevance of first aid to infection was pointed out by de Waal (1943) who found that the contamination of wounds and burns (particularly by streptococci) was more frequent when they were both "cleaned" and dressed by the first aid attendant than when they were merely dressed Colebrook and his colleagues (1945) advised that the primary object of all first aid to burns should be the prevention of streptococcal infections The burned surface should be covered with a sterile cloth or a recently ironed towel or sheet A non sterilized blanket should never be allowed to touch the burned area since blankets frequently harbour numerous bacteria including streptococci. The burn should not be washed and blisters should not be snipped.

CONTAMINATION IN HOSPITAL

The burns of many patients admitted to hospital become contaminated with pathogenic bacteria Does the patient contaminate the burn with his own bacterial flora or are the bacteria acquired from other sources? There is abundant evidence that the great majority of hospital infections are acquired by *cross infection* and that *self infection* by the patient's own flora plays only a limited part. The evidence upon which this is based is as follows.

(1) The percentage of burns containing various pathogenic organisms increases after admission to hospital

Examples—Cruickshank (1935) isolated haemolytic streptococci from 11 per cent of burns on admission to hospital but found that 66 per cent of them had acquired streptococci 3–6 days later Similar findings have been reported by Colebrook and his colleagues (1945) before an intensive drive against streptococci considerably reduced the incidence *Ps pyocyanea Proteus* and *Staph aureus* are also found more often after the patients have been in hospital days or weeks (Colebrook Duncan and Butterfield, 1947 Langohr Owen and Cope 1947 Colebrook Duncan and Ross, 1948 Jackson Lowbury and Topley 1951a and b Lowbury Topley and Hood, 1952 Korlof 1956)

CHAPTER 7

THE EPIDEMIOLOGY AND CONTROL OF INFECTION

DURING the first 30 or 40 years of this century few doctors concerned with burns attempted to prevent bacterial contamination although many recognized the results of infection Burned patients continued to be nursed and dressed in general surgical or even dermatological wards, where cross-infection was frequent Dunbar (1934) notes however that Lister's work influenced the treatment of burns in the Glasgow Royal Infirmary, where local antiseptic treatment with carbolic oil was introduced in 1869 Apparently the next attempt to control infection was that by Aldrich (1933), who found infection by streptococci to be very common and painted the burns with gentian violet and other chemotherapeutic dyes The first epidemiological study was that of Cruickshank (1935), who isolated haemolytic streptococci from the dust of burns wards and related this to the high rate of streptococcal infection

A major epidemiological study combined with a campaign against infection was launched by Colebrook in 1942 in the Burns Unit in Glasgow and later in Birmingham The discovery of the sulphonamides and penicillin had opened the door of chemotherapy, and Colebrook and his colleagues used these agents locally to control infection of burned skin This was part of a multiple attack against bacterial contamination based on the prevention of contact and airborne contamination and the elimination of bacterial reservoirs

EPIDEMIOLOGY

EARLY CONTAMINATION

The act of burning or scalding sterilizes the skin surface although it is possible for organisms deeply placed for example in hair follicles, to survive Most burns swabbed within an hour or two of injury are sterile (Colebrook and his colleagues, 1945) and bacteria cultured from a burned surface have probably been added after burning The frequency of haemolytic streptococci in the burns of 516 patients arriving at hospital at different times after injury was

investigated by Colebrook, Gibson and Todd (1945) in Glasgow This organism is not a normal skin microbe and is carried in the noses or throats of not more than 5 per cent of people Haemolytic streptococci were isolated from 4 per cent of burns arriving within 12 hours of injury from 23 per cent arriving between 12 and 24 hours, and from 42 per cent arriving after this. Therefore the patients could not have been responsible for contaminating most of these burns.

First-aid therapy—Bacteria may be added by well meaning friends, relatives and attendants. The relevance of first aid to infection was pointed out by de Waal (1943) who found that the contamination of wounds and burns (particularly by streptococci) was more frequent when they were both cleaned and dressed by the first aid attendant than when they were merely dressed Colebrook and his colleagues (1945) advised that the primary object of all first aid to burns should be the prevention of streptococcal infections The burned surface should be covered with a sterile cloth or a recently ironed towel or sheet. A non sterilized blanket should never be allowed to touch the burned area since blankets frequently harbour numerous bacteria including streptococci. The burn should not be washed and blisters should not be snipped.

CONTAMINATION IN HOSPITAL

The burns of many patients admitted to hospital become contaminated with pathogenic bacteria. Does the patient contaminate the burn with his own bacterial flora or are the bacteria acquired from other sources? There is abundant evidence that the great majority of hospital infections are acquired by *cross infection* and that *self infection* by the patient's own flora plays only a limited part. The evidence upon which this is based is as follows

(1) The percentage of burns containing various pathogenic organisms increases after admission to hospital

Examples—Cruickshank (1935) isolated haemolytic streptococci from 11 per cent of burns on admission to hospital but found that 66 per cent of them had acquired streptococci 3–6 days later Similar findings have been reported by Colebrook and his colleagues (1945) before an intensive drive against streptococci considerably reduced the incidence *Ps pyocyanea Proteus* and *Staph aureus* are also found more often after the patients have been in hospital days or weeks (Colebrook Duncan and Butterfield 1947 Langohr Owen and Cope 1947 Colebrook Duncan and Ross 1948 Jackson Lowbury and Topley 1951a and b Lowbury Topley and Hood 1952 Korlof 1956)

(2) The percentage of burns contaminated by various pathogens after admission is greater than the frequency of carriage on admission or among normal people

Examples—Cruickshank (1935) found that 6 5 per cent of burned patients carried haemolytic streptococci in their throats on admission, whilst 66 per cent of them had streptococci in their burns some days later *Ps pyocyanea* is rarely isolated from the normal skin or throat and is resident in only about 1–3 per cent of normal faeces (Sevitt 1945, Lowbury and Fox, 1954), but at times it colonizes the burns of 20–50 per cent of inpatients (Lowbury and Fox, 1954) The incidence of *Proteus* is more variable in normal faeces Sevitt (1945) found it in the stools of 16 per cent of children It may colonize the burns of many inpatients the faeces of whom did not contain this organism on admission The position is similar even with *Staph aureus*, which is carried in the nose or on the skin of 20–50 per cent of normal people, because its incidence on the burns of hospitalized patients is even more frequent Colebrook, Duncan and Ross (1948) found that on admission 20 per cent of patients carried *Staph aureus* in their noses, whilst 60–70 per cent of the severe burns acquired it at some time during the patient's stay in hospital Korlof (1956) isolated this organism from nearly 90 per cent of burns treated in hospital

(3) A multiplicity of types of a bacterial species are isolated from cases on admission whilst only one or two types may be dominant among those infected in hospital

This is the most conclusive evidence

Examples—The strains of *Str pyogenes* isolated from burns on arrival in hospital were of many serological Griffith types, whilst only one or two types were found among those infected in hospital (Colebrook and his colleagues, 1945) Serological typing of *Ps pyocyanea* isolated from burned arms on many in-patients showed that a particular strain was dominant whilst a number of types were found on burns which were infected on admission (Lowbury and Fox, 1954) Similarly, 80–90 per cent of staphylococcal strains isolated from in-patients are nowadays penicillin-resistant, and in Birmingham most of them belong to the 6/47 phage group, whilst most strains from recently admitted patients are sensitive to penicillin and belong to various phage groups (Lowbury, Topley and Hood, 1952)

(4) Pathogenic bacteria are often isolated from the air and dust of the wards and dressing rooms, and from blankets, clothing and other articles

This is considered further below

ROUTES, SOURCES AND VECTORS OF CROSS-INFECTION

Sources—Colonized burns and soiled dressings are the major reservoirs of infection in a burns unit In addition skin, nasopharyn-

geal and faecal carriers among the patients and staff are at times important additional sources of contamination

Routes and vectors.—Spread of cross-infection may occur in a variety of ways as follows

Airborne —Airborne transfer by bacteria-carrying particles of dust is one of the most important routes of contamination of large burns. Haemolytic streptococci, *Ps pyocyanea Staph aureus Proteus* and other organisms have been cultured from the dust and air of wards and dressing rooms (Cruickshank 1935 Bourdillon and Colebrook, 1946 Kashkin and his colleagues 1949 Lowbury and Fox, 1954 Korlof 1956) Bourdillon and Colebrook also demonstrated that a cloud of various microbes was dispersed into the air when dressings were removed from a burn when the patient s bed was made or when his blankets were moved (Fig. 44)

Droplet infection of wounds may occur and outbreaks of streptococcal infection have been related to sore throats or nasopharyngeal catarrh in patients or staff

Direct contact by unsterile instruments, by the contaminated fingers of a doctor nurse visitor or the patient and by contaminated blankets sheets, pyjamas, food trays, toys, washbasins and so on may at times be responsible Direct contact is probably more important than the airborne route in contaminating the smaller burns

Flies —In warm weather flies may transfer pathogenic bacteria.

Soaking of dressings —The copious weeping of recent burns may completely soak a thick cotton wool dressing and bacteria contaminating the bandage may grow through to the burn (Colebrook and Hood 1948) In the wards this is probably a not uncommon route of contamination The opposite process may also occur and bacteria from an infected burn may seep through to the bandage and contaminate the bedclothes and the air

Secondary self infection —The spread of bacteria often increases the proportion of healthy carriers among the patients (and staff) who may transfer the bacteria to their own burns Cruickshank (1935) found that the frequency of throat carriers of haemolytic streptococci among the patients rose from 6 5 per cent to 25 per cent within a few days of admission Lowbury and Fox (1954) showed that 20 per cent of inpatients became faecal carriers of *Ps pyocyanea* and Colebrook Duncan and Ross (1948) reported that nasal carriers of *Staph aureus* increased from 20 per cent to 75 per cent during their stay in the wards. Various workers, including Korlof (1956) have found that a particular strain of *Staph aureus* appeared in the nose of

patients before it appeared in their burns, as well as vice versa This is also true for *Str pyogenes* in the throat and *Ps pyocyanea* in the faeces This *secondary or delayed self-infection* by hospital strains of bacteria may be difficult to distinguish from cross-infection by the airborne or contact routes

Multiple routes —Various routes may be operating at the same time An infected burn may contaminate the air and thereby infect other burns or produce a carrier state in other patients Some of those with infected burns may become carriers, the carriers may infect their own burns, contaminate the atmosphere, transfer the organisms to other patients, produce new carriers and so on

Tracing the source of infection.—It is often not possible to discover which of the many routes of infection was responsible in a particular patient, and the ultimate source of a particular bacterial strain may be difficult or impossible to trace Sometimes the appearance of a new serological type makes it possible to trace its origin Thus Colebrook and Ross (1947) found that the fresh appearance of a type 1 *Str pyogenes* in the air of the dressing room was related to a small scab containing this organism on the elbow of the surgeon, and Lowbury and Fox (1954) on one occasion traced the spread of a new type of *Ps pyocyanea* to the admission of a patient containing this organism in his burn

CONTROL OF HOSPITAL INFECTION

It is not easy to avoid infection, and both Colebrook and his co-workers (Colebrook and his colleagues, 1945, Colebrook, Duncan and Butterfield, 1947, Colebrook, Duncan and Ross, 1948) and Kashkin and his colleagues (1949) emphasized that no single measure could prevent the contamination of burns A planned co-ordinated attack by doctors and nurses under the guidance of a clinical bacteriologist is necessary to prevent the spread of infection The principles of control are (1) elimination of reservoirs of pathogenic organisms, and (2) the prevention of contamination by airborne dust, droplet nuclei and contact By such means hospital contamination of burns by *Str pyogenes* has been greatly reduced in the Burns Unit in Birmingham

ELIMINATION OF BACTERIAL RESERVOIRS

Chemoprophylaxis and chemotherapy The main weapons are a number of antibiotics and other antibacterial agents which should be used (1) prophylactically on fresh burns to eradicate pathogens

which may contaminate them then or later and (2) therapeutically to eliminate established colonization

The antibiotics are powerful weapons but the power of some of them has waned in recent years owing to the emergence of resistant strains of bacteria (Chapter 6) Therapy may be either local or systemic generally the former is preferable as a high concentration of the agent is brought into contact with the bacteria, but systemic therapy has a place in the therapy of established streptococcal infection. The main present-day advantage of locally applied penicillin cream or powder is to protect fresh burns from *Str pyogenes* Penicillin even given systemically can no longer be relied on to eliminate streptococcal infection because the burns of in patients usually become colonized by penicillin-destroying bacteria, particularly penicillinase producing staphylococci Penicillin is now ineffective in preventing or eliminating contamination by hospital strains of *Staph aureus* Other agents such as the tetracyclines and erythromycin are very effective against *Str pyogenes* but recently tetracycline resistant streptococci (which may be eliminated by erythromycin at the risk of producing erythromycin resistant staphylococci) have been recognized (Lowbury and Hurst, 1956) Colonization of burns by *Staph aureus* cannot at present be controlled. The use of streptomycin, aureomycin, erythromycin and chloromycetin is followed by the emergence of resistant strains which spread by cross infection. Until recently the main obstacle has been the absence of an agent to which this organism does not become resistant, but newer agents (neomycin vancomycin and chlorhexidine) may be free from this defect The problem of prevention of antibiotic resistant strains is discussed below

Locally applied polymyxin E is effective in preventing and eliminating infection with *Ps pyocyanea* and resistant strains have not emerged (Jackson Lowbury and Topley 1951a)

There is no effective agent against *Proteus* because strains of this organism are either naturally resistant to most antibiotics or readily acquire resistance

Chemoprophylaxis with penicillin and polymyxin in the form of a cream containing both will prevent many burns from becoming contaminated with haemolytic streptococci and *Ps pyocyanea*

PREVENTION OF BACTERIAL CONTAMINATION

Chemoprophylaxis has already been considered Bacterial contamination must be controlled (1) in the dressing room and operating theatres where the burns are exposed and (2) between dressings and grafting operations that is in the wards Contamination by

patients before it appeared in their burns, as well as vice versa This is also true for *Str pyogenes* in the throat and *Ps pyocyanea* in the faeces This *secondary or delayed self-infection* by hospital strains of bacteria may be difficult to distinguish from cross-infection by the airborne or contact routes

Multiple routes —Various routes may be operating at the same time An infected burn may contaminate the air and thereby infect other burns or produce a carrier state in other patients Some of those with infected burns may become carriers, the carriers may infect their own burns, contaminate the atmosphere, transfer the organisms to other patients, produce new carriers and so on

Tracing the source of infection —It is often not possible to discover which of the many routes of infection was responsible in a particular patient, and the ultimate source of a particular bacterial strain may be difficult or impossible to trace Sometimes the appearance of a new serological type makes it possible to trace its origin Thus Colebrook and Ross (1947) found that the fresh appearance of a type 1 *Str pyogenes* in the air of the dressing room was related to a small scab containing this organism on the elbow of the surgeon, and Lowbury and Fox (1954) on one occasion traced the spread of a new type of *Ps pyocyanea* to the admission of a patient containing this organism in his burn

CONTROL OF HOSPITAL INFECTION

It is not easy to avoid infection, and both Colebrook and his co-workers (Colebrook and his colleagues, 1945, Colebrook, Duncan and Butterfield, 1947, Colebrook, Duncan and Ross, 1948) and Kashkin and his colleagues (1949) emphasized that no single measure could prevent the contamination of burns A planned co-ordinated attack by doctors and nurses under the guidance of a clinical bacteriologist is necessary to prevent the spread of infection The principles of control are (1) elimination of reservoirs of pathogenic organisms, and (2) the prevention of contamination by airborne dust, droplet nuclei and contact By such means hospital contamination of burns by *Str pyogenes* has been greatly reduced in the Burns Unit in Birmingham

ELIMINATION OF BACTERIAL RESERVOIRS

Chemoprophylaxis and chemotherapy The main weapons are a number of antibiotics and other antibacterial agents which should be used (1) prophylactically on fresh burns to eradicate pathogens

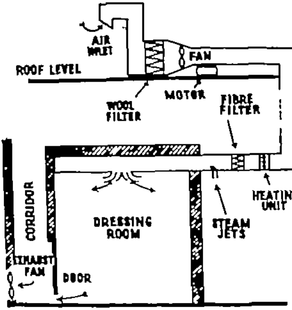


FIG 43 —Diagram of the air-conditioned dressing room for burned patients at the Burns Unit, Birmingham Accident Hospital Bacteria-free air is pumped in from the ceiling and air is removed at floor level. *By courtesy of Dr L Colebrook*

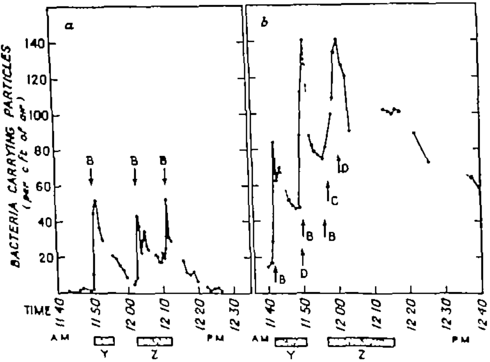


FIG 44 —Bacterial counts of the air in the air-conditioned dressing room during the dressing of burns on 2 patients (*a*) with ventilation plant on, and (*b*) with ventilation plant switched off Note that the bacterial count falls rapidly in (*a*) after each peak rise whilst there is a build up of air bacteria in (*b*) B = blankets gently disturbed C and D = other dressing procedures Hatched areas Y and Z show the time during which each patient was in the room *By courtesy of Dr L Colebrook and the Editor of the Lancet* (Bourdillon and Colebrook 1946.)

contact and droplet nuclei can be prevented during dressings and operations by a strict aseptic technique including the use of sterile gloves and instruments, the "no touch" technique of dressing, the wearing of masks, caps, gowns and boots, and the careful disposal of soiled dressings (*see Medical Research Council Memorandum*, 1951) A major contribution to the control of airborne contamination was that of Bourdillon and Colebrook (1946), who designed a special dressing room where a succession of patients can be dressed in a virtually bacteria-free atmosphere

Air-conditioned dressing station (Fig 43) —Air almost free of bacteria is pumped into the room at a slightly positive pressure The air enters through multiple diffusers at ceiling level after it has been ducted through coarse and fine filters and has been warmed and humidified The air escapes at ground level under the only door of the room into an airlock from which it is blown outside the hospital by an exhaust fan The air of the dressing room is changed about twenty times in an hour and this ensures the rapid removal of the bacteria which are dispersed during a dressing (Fig 44) This graph shows that bacterial contamination of the air of the room does not build up when a succession of patients are dressed as it does without air-hygiene of this kind To ensure a return to a bacteria-free atmosphere the ventilation is run for 5 minutes between the exit of one patient and the admission of the next Colebrook and his co-workers felt certain that the use of this dressing room played a major part in the considerable reduction of infection, particularly by *Str pyogenes*, which took place (Bourdillon and Colebrook, 1946, Colebrook, Duncan and Ross 1948, Colebrook 1950), but they pointed out that some of this improvement was also due to the use of penicillin prophylaxis The importance of air-hygiene was confirmed by Lowbury (1954), who examined the bacterial flora of two groups of comparable (but not severely burned) patients in a special trial The burns of one group were dressed whilst the ventilating plant was running and the others when it was off He found that the incidence of contamination with all pathogens (except coliform bacilli) was definitely less in those dressed in filtered air than in the others The value of filtered air was particularly striking in reducing the incidence of *Ps pyocyanea*

Operating theatre —Exposed burns are liable to become contaminated in the air of most operating theatres because these are usually ventilated by an exhaust system which sucks in dust-laden air from the floors and corridors of the hospital (Sevitt, 1949, 1953) Prevention of bacterial contamination can be facilitated by introducing a

Hoffmeister and Edgerton (1956) to be more rapid than the healing of similar burns covered by dressings It is uncertain whether this was related to relative freedom from infection and it may have resulted from the ability of pig epidermis to spread better under a dry scab than over a moist surface

The final place of exposure therapy in burns has not been settled, but three things are certain (1) it is not the treatment of choice to control hospital infection (2) it is the only practical therapy for burns of the face and perineum and (3) it cannot oust the closed-dressing method for most circumferential burns and for burns of the hand and foot In practice at the present time there is a place for both methods.

PREVENTION OF ANTIBIOTIC-RESISTANT STRAINS

The emergence of resistant organisms is a threat not only to burned and other hospitalized patients but also to the general population because resistant organisms are being transferred from hospitals to the general public For example the author has found that in 1955 about 80 per cent of staphylococcal infections acquired within the Birmingham Accident Hospital were due to penicillinase producing strains and about 10 per cent of staphylococcal infections treated in the hospital, but acquired at home or at work, were also due to resistant strains In Manchester Fairbrother (1956) reports that the latter incidence is over 30 per cent

The problem may be solved by the discovery of antibiotics against which bacteria, staphylococci for example, fail to develop resistance but to await such a solution may be to court disaster The present policy of *laissez faire* adopted by most hospitals in the use of anti biotics requires critical examination It is possible that a planned co-ordinated attack may achieve results and any policy adopted must affect the treatment of burned patients who are often important reservoirs of antibiotic resistant bacteria

The problem has been discussed by Lowbury (1955) and others, and among the possible recommendations are the following

(1) All antibiotics should be restricted to cases for which they are specially indicated and they should be used for the shortest possible time

(2) Antibiotics like streptomycin which readily induce resistance should be avoided when others are available

(3) The *combination* of two or more agents which must not be antagonistic requires detailed study Success in reducing the emergence of resistant strains of tubercle bacilli has been achieved by the combined use of streptomycin isoniazid and para amino-salicylic acid Theoretically the success of a combination depends first on the

positive-pressure ventilation system with filtered air as described above

Prevention of contamination in the wards—This is the more difficult problem and its solution lies not only in medical care but also in the correct design of centres where burned patients can be properly treated (Colebrook, 1950)

In addition to chemoprophylaxis the measures required are

(1) The covering of all burns until the next dressing, this may be difficult with burns on certain anatomical sites

(2) Early grafting of full-thickness-loss burns, re-epithelialization is the most effective barrier against bacteria Ross (1951) found that 67 per cent of burns grafted on the day of admission remained uncontaminated compared with 16 per cent grafted later than this

(3) Isolation of infected patients in single-bedded wards

(4) Suppression of dust in the wards by the oiling of blankets and floors and the use of vacuum cleaners in place of brooms Blankets should also be routinely sterilized at the time of laundering

(5) Elimination of flies

The exposure method of treatment—In reintroducing the old exposure method (but without heating) for the treatment of burns, Wallace (1949, 1951) claimed that one of the advantages of drying the burned skin was that it became unfavourable to the growth and multiplication of bacteria If this were true, dried exposed burns should not become reservoirs of pathogens Colebrook (1951) was not impressed with this therapy, and Lowbury, Crockett and Jackson (1954) carried out a bacteriological examination of the problem They found that burns of the trunk treated by exposure were colonized by streptococci and staphylococci just as often as trunk burns covered by dressings, that exposed burns of the face acquired *Str pyogenes* more often than burns of other areas, but that *Ps pyocyanea* and coliform bacilli were less commonly acquired by exposed burns Korlof (1956) reported that infection by *Ps pyocyanea* was relatively uncommon in burns treated by exposure but found that the incidence of other pathogens was frequent These reports are consistent with the known *in vitro* lethal effect of drying on *Ps pyocyanea* compared with the resistance of streptococci and staphylococci However, Lowbury and his colleagues showed that a heavy growth of *Ps pyocyanea* and other pathogens was obtained from the purulent exudate on the *deep* surface of the dried scab although the outer surface might yield only a scanty growth The healing of deep experimental burns in pigs treated by exposure was found by

REFERENCES

Colebrook, L. and Ross, W P D (1947) *Lancet* **2**, 792.
— Duncan, J M and Butterfield, W J H (1947) *Ibid.*, **1** 321
— — and Ross, W P D (1948) *Ibid* **1** 893
— Gibson, T., and Todd, J P (1945) In *Studies of Burns and Scalds* M R C Special Report Series No 249 Part I
— Clark, A. M Gibson, T., and Todd J P (1945) *Ibid* No 249 Part II
Cruickshank, R. (1935). *J Path Bact.*, **41** 367
Dunbar J (1934) *Glasg med. J* **122**, 239
Fairbrother R W (1956) *Lancet* **1** 716
Hoffmeister F S and Edgerton, M T (1956) *Ann Surg* **143** 49
Jackson, D McG Lowbury E J L., and Topley E. (1951a) *Lancet* **2**, 137
— — — (1951b) *Ibid.* **2**, 705
Kashkin, P N Kashkina, E. G., Mints, B M., and Neelova, N S (1949) *Khirurgia*, No 4 13
Korlof B (1956) *Acta chir scand*, Suppl 209
Langohr J L., Owen, C R. and Cope O (1947) *Ann Surg.*, **125**, 452.
Lowbury E. J L. (1954) *Lancet* **1** 292.
— (1955) *Brit med. J.*, **1** 985
— and Cason, J S (1954) *Brit med. J* **2**, 914
— and Fox, J (1954) *J Hygiene* **52**, 403
— and Hurst, L. (1956) *J clin. Path.* **9** 59
— Crockett, D J and Jackson, D McG (1954) *Lancet* **2**, 1151
— Topley, E., and Hood, A M (1952) *Ibid* **1** 1036.
Medical Research Council Memorandum (1951). No 11—Control of Cross-Infection in Hospitals.
Ross, P D R. (1951). Personal communication.
Sevitt, S (1945) *J Hygiene* **44**, 37
— (1949). *Lancet* **2**, 1075
— (1953) *Ibid.* **2**, 1121
Waal H L. de (1943) *Edinb med. J* **50** 577
Wallace A. B (1949) *Brit J plast Surg* **1** 232.
— (1951) *Lancet* **1** 501

presence of one antibiotic restraining the emergence of a strain resistant to the other, and secondly on the low frequency of bacteria which initially emerge resistant to any one antibiotic If in a bacterial population the number which initially become resistant to antibiotic A is very small (1 in many million) their multiplication will be prevented by the presence of antibiotic B and vice versa—if antibiotic B attacks a different metabolic function of the bacterium Moreover, the chance that a strain will emerge resistant both to A and B may be the multiple of the frequency of emergence to each and this may be very remote Current research suggests that combined therapy with novobiocin and erythromycin may be the answer to hospital infection with staphylococci

(4) Serious consideration should be given to the restriction of the routine use of any one antibiotic within a hospital to a limited period (say 1–3 months) and the prohibition of other agents except for special cases during this period In this plan a period of use of antibiotic A would be followed by an interval during which antibiotic B is used routinely and A (and other agents) prohibited, B would be followed by C, during the use of which B and A and the other agents would be prohibited, and so on until A is used again Such a plan might be successful because there is evidence that the emergence of some resistant strains may not occur until months after the introduction of the antibiotic For example, Lowbury and Cason (1954) found that erythromycin-resistant strains of staphylococci did not appear in the Burns Unit until months after the introduction of the agent Success would depend on a fall in frequency of resistant strains to antibiotics not in routine use at the time and on a delay in the emergence of resistant strains to the antibiotic in use It would also depend on the full co-operation of all the hospital medical staff

(5) Finally the use of one or perhaps two particular antibiotics should be reserved for patients seriously ill with an infection due to a sensitive organism resistant to all other agents The antibiotic chosen should be one to which resistant strains of staphylococci have not yet emerged or are few within the hospital For example, if the incidence of erythromycin-resistant staphylococci is only 1 or 2 per cent (as it is at present in the Birmingham Accident Hospital) this antibiotic should be reserved for serious infections by sensitive organisms which are resistant to all other antibiotics

REFERENCES

Aldrich, R H (1933) *New Engl J Med*, 208, 299
Bourdillon, R B, and Colebrook, L (1946) *Lancet*, 1, 561, 601
Colebrook, L (1950) *A New Approach to the Treatment of Burns and Scalds* London, Fine Technical Publications
— (1951) In *Symposium on Burns*, p 124 Washington, National Research Council
— and Hood, A M (1948) *Lancet*, 2, 682

TABLE I

APPROXIMATE MORTALITY IN BURNED PATIENTS WITH VARIOUS COMBINATIONS OF AGE AND PERCENTAGE AREA BURNED (BASED ON 2,807 IN PATIENTS 1942–1952)

% Body area burned	Age in years																
	0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84
77 +	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0
73–77	0 9	0 9	0 9	0 9	0 9	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0
68–72	0 9	0 9	0 9	0 9	0 9	0 9	0 9	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0
63–67	0 8	0 8	0 8	0 8	0 9	0 9	0 9	0 9	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0
58–6	0 7	0 7	0 7	0 7	0 8	0 8	0 8	0 9	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0
53–57	0 6	0 6	0 6	0 6	0 7	0 7	0 8	0 8	0 9	1 0	1 0	1 0	1 0	1 0	1 0	1 0	1 0
48–52	0 5	0 5	0 5	0 5	0 6	0 6	0 7	0 7	0 8	0 9	1 0	1 0	1 0	1 0	1 0	1 0	1 0
43–47	0 4	0 4	0 4	0 4	0 4	0 5	0 5	0 6	0 7	0 8	0 9	1 0	1 0	1 0	1 0	1 0	1 0
38–42	0 3	0 3	0 3	0 3	0 3	0 4	0 4	0 5	0 6	0 7	0 9	0 9	1 0	1 0	1 0	1 0	1 0
33–37	0 2	0 2	0 2	0 2	0 2	0 3	0 3	0 4	0 5	0 6	0 8	0 9	0 9	1 0	1 0	1 0	1 0
28–32	0 1	0 1	0 1	0 1	0 2	0 2	0 2	0 3	0 4	0 5	0 6	0 8	0 9	1 0	1 0	1 0	1 0
23–27	0 1	0 1	0 1	0 1	0 1	0 1	0 1	0 2	0	0 3	0 4	0 6	0 8	0 9	1 0	1 0	1 0
18–22	0	0	0	0	0	0	0 1	0 1	0 1	0 2	0 3	0 4	0 6	0 8	0 9	1 0	1 0
13–17	0	0	0	0	0	0	0	0	0 1	0 1	0 2	0 3	0 4	0 6	0 7	0 8	0 9
8–12	0	0	0	0	0	0	0	0	0	0	0 1	0 1	0 2	0 4	0 5	0 6	0 7
3–7	0	0	0	0	0	0	0	0	0	0	0	0	0 1	0 2	0 3	0 4	0 5
0–2	0	0	0	0	0	0	0	0	0	0	0	0	0	0 1	0 1	0 2	0 3

The figures are proportional mortalities approximated to single place of decimals Thus 0 5 is equivalent to 50 per cent mortality and 1 0 means "most probable mortality greater than 95 per cent

By courtesy of Dr J P Bull and the Editor of the Annals of Surgery (Bull and Fisher 1954)

prognosis when the burns are superficial than when they are deep The risks of circulatory and renal failure during the first 2 or 3 days (shock period) are probably about equal but when these have been overcome the subsequent risks are less among those with partial skin loss burns Healing is complete in these within 2 or 3 weeks, whilst serious hazards particularly bacterial infection continue among those with sloughing and granulating full thickness-loss burns The location of burning is of prognostic interest mainly in patients with burns of the respiratory tract in whom laryngeal oedema and ulcero-membranous laryngo-tracheitis are special hazards.

Measurement of the area burned —The burn is measured as a percentage of the total body area In most subjects the areas of various parts of the body form similar proportions of the total surface area and if these are known the percentage area burned can be estimated Berkow s (1924 1931) figures are generally used and in adults the area relationships between different parts of the body are as follows each part being expressed as a percentage of the total body area

CHAPTER 8

MORTALITY AND CAUSES OF DEATH

A PROPER study of mortality and causes of death in burned patients not only has an intrinsic value but also has important practical applications Knowledge of the main causes of illness and death exposes the main problems requiring solution, and statistical evaluation of mortality may help to assess the worth of a new remedy or therapy

Death or survival is influenced by factors which exist before burning as well as those related to and following the injury The most important of the former are age, health and individual tolerance or resistance, and of the latter the severity of burning and subsequent therapy The interval between burning and commencement of anti-shock therapy is important and sometimes the site of burning Together the various factors determine the course of the burn illness and the changes and complications such as shock, infection, anaemia, renal failure, hypoproteinaemia and loss of weight which may occur The presence and severity of these largely govern the severity of the burn illness and commonly determine whether or not the outcome will be fatal

MORTALITY ANALYSIS

It is generally agreed that the risk of dying increases with the severity of burning and with advancing age At one time few patients with burns involving more than one-third of the body area survived, but this is now no longer so For example, with modern treatment the majority of children with burns involving up to 40 or 50 per cent of the body surface should survive and the outlook of those more extensively burned is not hopeless (Table I) Death is not inevitable even in patients with burns extending over 70 or 80 per cent of the body area

The severity of burning depends on the extent and depth of the injury Extent is easier to measure than depth (Chapter 4) and in most accidental burns it is probably the more important of the two Nevertheless subjects of the same age and percentage area burned and treated under the same conditions have a better ultimate

and area burned must be responsible such as depth of burning, the previous health of the patients, the frequency of organic disease among them (*vide infra*) and the ill-defined concept of individual resistance

The statistical evaluation was further developed by Bull and Squire (1949) and Bull and Fisher (1954) using the Probit technique The essence of this method was the conversion of the sigmoid mortality curve for each age group (0–14 15–44 45–64 and more than 65 years) into a number of straight lines The results were then co-ordinated to show mortality at any age since age grouping is artificial and ageing is a continuous process A series of contour lines were produced which divided zones of equal mortality varying from 10 per cent to 90 per cent against age and percentage area burned each of the contour lines being derived mathematically from the appropriate Probit line Finally a table or grid was constructed which shows the percentage mortality for groups of patients with any given combination of age and percentage burned area (Table I) in this mortality is expressed as a fraction so that 0 5 means 50 per cent mortality The meaning of the figures was extended to give the probability of death in *individual* patients This is probably permissible for retrospective statistical analysis of groups of individuals but its value for single patients is limited The number of deaths to be expected among a group of patients differing in age and area burned can be calculated by adding the individual fractions for each patient according to his age and area burned. This probability total can be compared with the number of deaths actually found When the actual number is significantly more or less than the expected number some factor other than age and area burned is responsible This factor might or might not be a different method of treatment.

The method can be used to help evaluate a new therapy with the provisos that other conditions remain unchanged and that the *post hoc ergo propter hoc* fallacy is avoided The method has been useful in Birmingham in the assessment of dextran as a substitute for plasma (quoted by Bull and Fisher 1954) and in appraising the fluid requirements of patients (Evans and his colleagues, 1952) It was also claimed to have been of value in assessing the use of whole blood plus buffered saline transfusion in lieu of plasma (Moyer 1953) but the results are doubtful since the different therapies were carried out in different hospitals where other conditions may have varied greatly The method is of help in comparing the mortality from burns in different hospitals and at different times in the same hospital (*vide infra*) The grid table and the statistical technique upon which it is based is useful but like all statistical methods its value is limited by the factors (age and percentage burn area) upon which it is based

head, 6, trunk and neck, 38 (anterior surface 20), upper limb 9 (hand 2 5), lower limb 19 (thigh 9 5, leg 6 5, foot 3) per cent

This was further simplified by Wallace (1951) into the "rule of nines" which has the advantages of being easily remembered as well as being reasonably accurate The head and each upper limb are each regarded as forming 9 per cent of the body area whilst the front of the trunk, back of the trunk and each lower limb are considered as 18 per cent of the total area

These figures do not apply to children, in whom the head forms a larger proportion and the lower extremities a smaller part of the body area

Statistical measurement of mortality.—The over-all case mortality has often been reported in series of in-patients, but these reports are almost worthless since the risk of dying depends so much on the extent of burning and on the age of the patient It is fruitless to compare the case mortality rates in two hospitals or even the rates in the same hospital at different periods without taking into account the different ages of the patients and the extents of burning among the patients in the different age groups

Surveys of mortality in terms of percentage area burned and age have been made by Lutken (1937) in Copenhagen and later in the same hospital by Perdrup (1950), by Bull and Squire (1949) and Bull and Fisher (1954) in Birmingham, by Postnikov (1949) in the Soviet Union and by Moyer (1953) in the U S A The analyses are based on a division of burned in-patients into different age-groups each of which is subdivided into subgroups of different extents of burning The mortality rates in each subgroup are then calculated

When the percentage mortality in each age-group is plotted graphically against the percentage area burned a sigmoid curve is produced This important relationship was originally demonstrated by Clarkson and Lawrie (1946) The percentage mortality at first rises slowly as the area burned increases, then steeply, and finally slowly again as 100 per cent mortality is approached The slow initial and final parts produce the sigmoid shape, and mean, first that among patients with relatively small burns there is a minority more susceptible to burning and its complications than the others, and secondly that among patients with more extensive burns in whom the mortality approaches 100 per cent there are a few less susceptible than most In other words the sigmoid relationship statistically exposes variations in susceptibility and resistance to death among a burned population of the same age Although this variation is not surprising its causes are not always easy to determine Factors other than age

found that in centres in the U S A the mortality in recent years was much the same as in Birmingham. He thought that present-day mortality had hardly improved from the figures reported by Sneve (1905) who did not use plasma but gave large volumes of saline intravenously orally and per rectum during the shock period. On the other hand Perdrup (1950) who compared the mortality figures in a Copenhagen hospital during 1938–48 with the 1915–35 figures reported by Lütken (1937) from the same hospital concluded that modern principles of treating shock infection, and so on had yielded good results The mortality data for children reported by Lütken (1937) Farmer (1943) Rosenqvist (1947) and Perdrup (1950) were analysed by Bull and Fisher (1954) and compared with the Birmingham figures The conclusion was made that there was a progressive improvement in mortality until the nineteen forties but that there has been little or no improvement since the 1942–47 period This is in spite of apparently progressive improvements of treatment, which in Birmingham include increased transfusion of blood better control of plasma and electrolyte therapy the use of new antibiotics and other measures

The treatment of shock seems to have advanced more than the power to keep the patients subsequently alive Nowadays more patients with extensive burns survive the shock period, and perhaps the subsequent week or two only to die later from other complications In Birmingham the mean survival times of fatally burned patients is now two or three times as long as in 1945–47 Fatal cases survive an average of three weeks or longer compared with one or two weeks in 1945–47 8 out of 20 patients died within 48 hours in 1945–47 compared with 5 out of 41 in 1951–52. Moyer reports similar figures and concludes that shock therapy is no longer a problem but that there is still much to be done to increase the effectiveness of other therapy

CAUSES OF DEATH

A variety of functional and organic sequelae can be lethal or contribute to death after burning but the causes of many deaths are poorly understood Sometimes a particular complication is dominant but often a number are present and it may then be difficult to decide which if any played the major lethal role Many derangements of function are interlinked and influence one another sometimes to the detriment of the patient, but when a particular change or complication has dominated the scene clinically (for example circulatory failure from oligaemia anuria or pneumonia) it is reasonable to regard it as the major cause of death Occasionally death results from

and it cannot be expected to yield clinical or pathological information It must be emphasized that the table should not be used to influence the treatment of individual patients In particular, when the table shows a mortality of, or approaching, 100 per cent (1 0) it does not mean that the patient's life cannot be saved by active therapy, since he may be one of the few who, according to the sigmoid curve, differs from the majority

Young children and adults.—It is widely believed that infants and young children have a higher mortality than older children and young adults, but the analysis of Bull and Fisher (1954) does not support this The mortality rate among 1,041 children under 4 years was similar to that among older children with burns of similar extent The results indicated that the mortality in all patients up to about 30 years is similar for burns of similar extent and that above this age the mortality gradually increases

Organic disease.—The frequency of serious organic disease among fatally burned civilians is surprisingly high and this influences the prognosis, particularly of the elderly Jackson (1953) reported that nearly a third of 104 subjects who died after burning had pre-existing organic disease and that in 10 of them death was due to this and not to the burn Organic lesions found by the author at necropsy in burned individuals include cerebral haemorrhage, coronary atheroma and thrombosis, evidence of hypertension, carcinomas of the lung, stomach and bowel, Paget's disease of bone, various cerebral tumours, miliary and other forms of tuberculosis and subacute nephritis Some of these patients and others like them are included in the analysis by Bull and Squire (1949) and Bull and Fisher (1954) and therefore influence the mortality figures in Table I The burning accident not infrequently results from a state of unconsciousness or weakness due to a pre-existing lesion, and if this was from a cerebral or cardiac attack it might itself have proved fatal or have largely contributed to death The prognosis in burned patients therefore is partly determined by the presence, severity and nature of organic disease, particularly among elderly patients in whom pre-existing disease is not uncommon The mortality figures in Table I do not take into account the previous health of the patients, and the true mortality figures for previously healthy elderly subjects are less than those recorded Bull and Fisher were conscious of this and proposed a method of correcting the table

Changes in mortality and length of survival—Mortality figures published from hospitals at different times have been analysed by Perdrup (1950), Moyer (1953) and Bull and Fisher (1954) Moyer

12 and 48 hours after burning but death may be delayed until the third fourth or fifth day In recent years the frequency of death from oligaemia has been reduced because plasma and other fluids are transfused Occasionally circulatory failure cannot be reversed by transfusion either because of a delay in treatment or through early inadequate therapy or for obscure reasons and death occurs from *irreversible* shock. Some extensively burned patients die obscurely during the first few days although the plasma and red cell volumes may be maintained within normal limits renal function is adequate and there is no evidence of a serious electrolyte metabolic or other physiopathological disturbance

Complications of fluid therapy are sometimes responsible for death It has been said that the administration of fluid deficient in colloid may provoke pulmonary oedema, and excessive or prolonged transfusion may overload the circulation when the burn oedema is being absorbed

Acute anaemia or acute haemolytic jaundice are sometimes serious and appear to contribute to death during the shock period or within the next few days

(2) Deaths from acute disturbances of other vital functions.—Vital disturbance of other main body functions can cause or contribute to death particularly hyperpyrexia acute respiratory distress and renal failure

Hyperpyrexia —Some patients develop one or more episodes of high fever particularly during the first few days the body temperature reaching 106 F (41 1 C) This is nearly the minimal lethal cerebral temperature in rabbits (42°–43 C) (Chapter 2) so that the results of body hyperthermia analogous to those of heat stroke may contribute to death

Acute respiratory distress —This is not uncommon in children and may clinically resemble bronchopneumonia its cause is obscure but when death occurs congestive atelectasis is often found Children dying in this manner generally succumb during the first week

Renal failure is relatively frequent and commonly sets in soon after burning, but death at this stage is generally related to shock Uraemia develops during the next few days and death ensues a week or two after burning Renal failure may be oliguric or non-oliguric

Acute encephalopathy is an obscure and relatively infrequent complication in children being associated clinically with convulsions and coma and pathologically with a variety of lesions

Adrenal failure —Few if any deaths occur from this cause

an unusual complication, such as acute encephalopathy or haemorrhage from a perforation of a post-burn duodenal ulcer, and sometimes undesirable complications of therapy are responsible or contributory.

On the other hand, studies during life and at necropsy may not reveal a functional or organic cause of death which is intellectually satisfying Jackson (1953) considered that in 7 out of 104 fatally burned patients the cause of death was undiagnosed, but the number was probably greater than this because 9 other patients were regarded as dying from unspecified cardiac or cardio-renal failure and some of the 19 cases of pneumonia listed may have been terminal rather than terminating These difficulties raise the important difference between mode of dying and cause of death, but they are not confined to burned patients Similar problems extend through the realms of pathology and medicine and are reflections of biological complexities and current ignorance

The causes of death listed below are considered in more detail in other chapters

Classification —Neglecting pre-existing disease, which has already been discussed and causes associated with special kinds of burns (electrical, chemical, and the like), the causes of death may be grouped into those related to (1) shock and acute circulatory failure, (2) acute disturbance of other vital functions, (3) complications of an extensive raw skin area, (4) miscellaneous complications, and (5) therapeutic complications

Most deaths are attributable to oligaemic shock or to infective complications Burn toxaemia has been omitted as a cause of death although it was previously considered of great importance

(1) Deaths related to shock and acute circulatory failure.—These usually occur during the first 2 or 3 days and are still frequent Gibson (1945) found that 19 out of 30 deaths occurred during the shock period, and even in 1953 Jackson reported that 40 out of 104 deaths were attributable to shock

Primary or nervous shock from pain, fright, or similar cause rarely results in death, but when it does death is rapid, within minutes or hours Patients exposed to the high ambient temperature of a fire in a building or other confined space might develop a rapid *hyperpotassaemia*, and asphyxia from *carbon monoxide poisoning* is also a potential cause of death in such an environment These patients rarely reach hospital alive

Secondary shock or peripheral circulatory failure from oligaemia is the usual early hazard and generally causes a fatal outcome between

12 and 48 hours after burning but death may be delayed until the third fourth or fifth day In recent years the frequency of death from oligaemia has been reduced because plasma and other fluids are transfused Occasionally circulatory failure cannot be reversed by transfusion either because of a delay in treatment or through early inadequate therapy or for obscure reasons and death occurs from *irreversible* shock Some extensively burned patients die obscurely during the first few days although the plasma and red cell volumes may be maintained within normal limits renal function is adequate and there is no evidence of a serious electrolyte metabolic or other physiopathological disturbance

Complications of fluid therapy are sometimes responsible for death It has been said that the administration of fluid deficient in colloid may provoke pulmonary oedema, and excessive or prolonged transfusion may overload the circulation when the burn oedema is being absorbed

Acute anaemia or acute haemolytic jaundice are sometimes serious and appear to contribute to death during the shock period or within the next few days.

(2) **Deaths from acute disturbances of other vital functions.**—Vital disturbance of other main body functions can cause or contribute to death particularly hyperpyrexia acute respiratory distress and renal failure

Hyperpyrexia —Some patients develop one or more episodes of high fever particularly during the first few days the body temperature reaching 106°F (41 1 C) This is nearly the minimal lethal cerebral temperature in rabbits (42°–43 C) (Chapter 2) so that the results of body hyperthermia analogous to those of heat stroke may contribute to death

Acute respiratory distress —This is not uncommon in children and may clinically resemble bronchopneumonia its cause is obscure but when death occurs congestive atelectasis is often found Children dying in this manner generally succumb during the first week

Renal failure is relatively frequent and commonly sets in soon after burning but death at this stage is generally related to shock Uraemia develops during the next few days and death ensues a week or two after burning Renal failure may be oliguric or non-oliguric

Acute encephalopathy is an obscure and relatively infrequent complication in children being associated clinically with convulsions and coma and pathologically with a variety of lesions

Adrenal failure —Few if any deaths occur from this cause

(3) Deaths from complications of an extensive raw skin area—Infection, anaemia, hypoproteinaemia, pyrexia and loss of weight are the major results of an extensive sloughing or granulating area of full-thickness-loss burning, and commonly coexist Hypoproteinaemia may result in a generalized oedema

Infective complications are frequent, often causing death two to six weeks after burning Bronchopneumonia and septicaemia are the most frequent causes, and sometimes the invasion of pyogenic bacteria results in pyaemia or ulcerative endocarditis Other occasional infections are pyogenic meningitis and pyelonephritis Tetanus is very rare in Birmingham and deaths from burn scarlatina and erysipelas are nowadays very uncommon

In the past, deaths from infection were less common than they are today, but this is because many patients who previously would have died from the complications of oligaemia now survive two weeks or longer only to succumb to infection For example, Erb, Morgan and Farmer (1943), who analysed 61 fatalities occurring between 1920 and 1942, found that only 7 of them died of infection, whilst Jackson (1953), who reported on cases occurring between 1948 and 1952, found that 26 out of 104 died from bacterial infections—mainly pneumonia and septicaemia Liedberg, Reiss and Artz (1954), reporting on recent cases, particularly stressed the frequency of septicaemia and related 16 out of 35 deaths to this cause

(4) Deaths from other complications—*Respiratory tract burns* may cause death from laryngeal oedema or through the development of a membranous laryngo-tracheitis

Pulmonary embolism, from deep vein thrombosis of the lower limbs is an incidental complication particularly in elderly people

Haemorrhage from an acute post-burn duodenal ulcer occasionally causes death, death from perforation is rare

(5) Deaths from therapeutic complications or accidents—Complications of fluid therapy have already been mentioned Other undesired lethal complications are hepatic necrosis from the local use of tannic acid, agranulocytosis from sulphonamides and enterocolitis from systemic aureomycin therapy Deaths during operation and under anaesthesia, from post-operative collapse and from air embolism related to intravenous therapy also occur

REFERENCES

Berkow S G (1924) *Arch Surg.*, **8**, 138
— (1931) *Amer J Surg* **11** 315
Bull J P., and Squire J R. (1949) *Ann Surg* **130** 160
— and Fisher A. J (1954) *Ibid.*, **139** 269
Clarkson, P and Lawrie R. S (1946) *Brit J Surg* **33**, 311
Erb I. H. Morgan, E. M and Farmer A W (1943) *Ann Surg* **117** 234
Evans, E. I Purnell O J., Robinett, R. W Batchelor A. and Martin, M. (1952) *Ann Surg.*, **135**, 804
Farmer A. W (1943) *Amer J Surg* **59** 195
Gibson, T (1945) In *Studies of Burns and Scalds* M R C. Special Report Series No 249 192.
Jackson D McG (1953) *Ann. R. Coll Surg Engl* **13**, 236
Liedberg, N C F Reiss E. and Artz, C P (1954) *Surg Gynec Obstet.*, **99** 151
Lutken, P (1937) *Ugeskr læg* **99** 409 (Quoted by Perdrup 1950)
Moyer C A. (1953) *Ann Surg* **137** 628
Perdrup A. (1950) *Acta chir scand* **100**, 136.
Postnikov B N (1949) *Khirurgia*, No 4 9
Rosenqvist, H (1947) *Acta chir scand* 95 Suppl 124
Sneve, H. (1905) *J Amer med Ass* **45** 1
Wallace, A. B (1951) *Lancet* **1** 501

CHAPTER 9

BURN SHOCK: HAEMODYNAMIC AND CIRCULATORY EFFECTS

THERE has been much controversy over the definition of burn shock, which has been divided into *primary* or neurogenic shock (Chapter 11) and *secondary* shock due to a loss of circulating blood volume The expressions primary and secondary are unsuitable terms, because neurogenic shock in man is rare after burning and the first symptoms to develop are due to the so-called secondary kind Moreover, the symptoms of secondary shock, whilst commonly delayed for a few hours, may begin more quickly, particularly when there is a rapid development of oligaemia in very extensively burned patients or when there is a deficiency in vasomotor compensation

There is now general agreement that the initiating factor in shock from burns, trauma and haemorrhage is a loss of blood volume, and in burns this is mainly from a loss of plasma into the burned area (Chapter 10) The oligaemia leads to a diminished cardiac output, a diminished flow of blood through the body and consequently a reduction in the carriage of arterial oxygen Vasoconstriction occurs, increases the over-all peripheral resistance and maintains the arterial blood pressure for a time The increased peripheral resistance, which is greater after extensive burns than after other causes of oligaemic shock, means that the circulation may be reduced to a fraction of normal in certain tissues such as the skin, kidneys, muscles and probably the liver and alimentary tract, but the heart work is increased This vasomotor compensation maintains the circulation through the coronary vessels and the brain, it is aided by a reduction of the oligaemia through the movement of water from the tissues into the blood stream (Chapter 10) but it is hindered by the increased blood flow through, and the capillary stasis in, the burned areas When compensation is insufficient and the oligaemia is untreated the mechanisms for maintaining the blood pressure fail, the circulation through the myocardium and the brain decreases, the arterial pressure falls further and the circulation is in great danger The degree to which the compensatory mechanisms are strained in patients with large burns is shown by the fact that sudden circulatory failure may be pre-

cipitated by pain excessive cooling or heating, alcohol operation and even changes in posture

CIRCULATORY DYNAMICS

The haemodynamic effects of traumatic shock and haemorrhage were studied during World War I by Bayliss and his colleagues (1919) and the existing knowledge was analysed by Cannon (1923) in his classical monograph during World War II investigations were carried out by Grant and Reeve (1951) and by Cournand Gregersen Richards and their co-workers (Cournand and his colleagues 1943 Richards, 1943–44 Lauson Bradley and Cournand 1944 Noble and Gregersen 1946) Although relatively few burned patients were studied by these workers the results indicate that the main haemodynamic generalizations derived from injured patients are applicable to burned subjects and this is supported by the clinical and experimental findings of other workers in the field of burns Certain technical advances have played a major part in unfolding the circulatory changes in shocked patients The development of the Evans blue (T1824) dye method has permitted estimations of plasma volume and more recently of cardiac output The availability of radioactive isotopes (radiophosphorus radiochromium) has allowed independent measurement of the red cell volume The development of cardiac catheterization has permitted the measurement of right auricular pressure and the oxygen and carbon-dioxide contents of mixed venous blood and the cardiac output has also been measured by concurrent estimations of the respiratory gases and the arterial blood using the Fick principle

Cardiac output.—Simultaneous measurement in recently burned patients of plasma and blood volumes cardiac output right auricular and arterial pressures have shown that the changes which occur are closely related A reduction in the circulatory blood volume largely from plasma oligaemia is linked with a considerable fall in the cardiac output even though the blood pressure may not have fallen Richards (1943–44) reported the mean findings in a group of 9 recently burned patients in whom haemoconcentration due to loss of plasma had developed The total blood volume expressed in terms of the average 70 kilogram man with 1 73 square metres of body surface had fallen to 3 4 litres (mean normal 5 2 litres) whilst the cardiac output was only 2 9 litres per minute (mean normal 5 4) The low cardiac output was confirmed by Hardy and his colleagues (1955) in a group of extensively burned adults. Before commencing therapy the cardiac output had fallen to between 2 0 and 4 6 litres per minute in the different patients In burned dogs Gilmore and

Handford (1956) found that a considerable reduction in cardiac output commenced within 15–60 minutes after burning and they believed that its onset preceded a significant reduction in the plasma volume This conclusion is open to criticism on technical grounds Plasma volume was measured by the Evans blue dye technique, and after burning the degree of oligaemia is under-estimated because some of the plasma-bound dye rapidly enters the burn exudate (*see* Chapter 3)

It is important to consider some of the implications of a low cardiac output In the "average" man (*vide supra*) with a resting cardiac output of about 5 4 litres per minute, the renal blood flow is about 1,500 millilitres that of the brain is about 1,300 millilitres, and the flow through the splanchnic bed and liver is about 1,500 millilitres per minute Of the remaining 1,100 millilitres per minute the muscles receive 600 millilitres, the skin 200 millilitres, and the heart 60 millilitres, leaving merely 200–300 millilitres of blood per minute for the rest of the body

If it is true, as generally believed, that the coronary and cerebral arteries contain few if any vasoconstrictor fibres, the blood flow through them would depend upon their calibre and the blood pressure, the latter depending on the over-all vasoconstriction in other vascular beds When the blood pressure is normal and even when the cardiac output is decreased the cerebral and coronary circulation would be normal or near normal because cerebral and coronary vasoconstriction does not occur This must greatly reduce the blood flow to the rest of the body For example, if the cardiac output falls to 3 litres per minute, only about 1,600 millilitres per minute would be available for distribution to the kidneys, liver, muscles, skin and other tissues, the total resting blood flow of which is normally about 4 litres per minute The renal blood flow may fall to 10 per cent of normal or less, that of the unburned skin is markedly reduced, there is evidence in dogs that the liver blood flow decreases soon after burning (Dobson and Warner, 1954), and although no figures are available for the blood flow through the muscles it is safe to assume that this is also considerably lowered

The reduction in hepatic circulation is supported by the observations of Abell and Page (1943), who found that in the splanchnic bed of scalded dogs and cats the vessels became greatly narrowed until the arterial and venous flow almost ceased (*vide infra*) Moreover, burned patients differ from subjects with traumatic or haemorrhagic shock in that the total blood flow through the burned area is increased and considerable trapping of blood in the capillaries may be present (Chapter 3) These changes further reduce the available blood for

circulation to the kidneys, liver and other organs This probably explains why the degree of vasoconstriction is greater in burned than in other injured patients

The fall in cardiac output is also associated with a rising pulse rate so that the stroke volume of the heart is considerably lessened This produces the well known pulse found in shock—rapid feeble and of greatly diminished volume Arterial tracings show a sharp rise of pressure during systole, a rapid collapse during diastole and a lowered pulse pressure Bradycardia is exceptional

Right auricular pressure and venous return.—Richards (1943–44) reported that the fall in cardiac output was associated with a moderate but definite fall in the right auricular pressure even though the femoral artery pressure was about normal The fall was less than that found in patients with traumatic or haemorrhagic shock but this was attributed to bandaging around the thorax which may have raised the intrathoracic pressure The reduced right auricular pressure indicates a decreased venous return either from oligaemia, peripheral venospasm or both A reduced venous flow is supported by the observation of Barac (1946) who found that the flow through the external jugular vein of dogs was diminished after burning though the blood pressure was normal The observation of active venoconstriction in the mesentery (Abell and Page 1943) as well as the clinical observations of spasm in peripheral veins indicates that venoconstriction participates in reducing the venous return

It has been asserted that the fall in right auricular pressure pre cedes the fall in cardiac output, and that the latter results from a diminished venous return in other words that Starling s law is applicable to oligaemic shock The observations of Gilmore (1955) and Gilmore and Handford (1956) do not support this Repeated measurements of the right atrial pressure and cardiac output in burned dogs showed that the early pressure changes were variable and might be increased unchanged or decreased even though the cardiac output had fallen Some hours later there was a gradual decline in the intra atrial pressure The haemodynamic factors initiating the fall in the cardiac output are not fully understood and it is possible that vasoconstriction plays an important role Certainly when burn shock is established there is both a decreased venou return and a considerable increase in over all peripheral resistance

Changes in blood pressure—An early and temporary rise of blood pressure has been observed clinically and experimentally the hypertension lasts a variable period up to a few hours after which the blood pressure falls to normal and then below normal (Kabat

and Hedin, 1942, Brown, 1945, Rosenqvist, 1947, Morrison, 1947) Brown (1945) found that 20–25 per cent of 68 patients examined within 3 hours of burning had a systolic pressure greater than normal, sometimes reaching 160–200 millimetres of mercury, and Morrison (1947) noted that 21 out of 27 recently burned children were hypertensive at first The early pressure rise might be explained as the result of fright or excitement, but this explanation is not always acceptable since hypertension may be found in sleeping or co-operative children The initial rise in blood pressure may be reflexly induced through stimuli from the burned area, because Kabat and Hedin (1942) showed that prior transection of the spinal cord in cats prevented the postburn phase of hypertension Hypertensive episodes may also occur during transfusion therapy

Even when a phase of hypertension is absent the blood pressure may not fall for hours but remains within normal limits although oligaemia is considerable, haemo-concentration is established and the cardiac output is reduced (Johnson and Blalock, 1931, Keeley, Gibson and Pijoan, 1939, Black, 1940, Brown, 1945) Noble and Gregersen (1946) found that cardiac output and plasma volume may be considerably lowered whilst blood pressure remained normal

A phase of normotension also occurs in traumatic shock and after acute blood loss It is associated with an over-all increase in peripheral resistance from vasoconstriction which favours the maintenance of a normal arterial pressure in the presence of a reduced circulating blood volume A normal (or raised) blood pressure does not mean that transfusion is unnecessary or may be delayed On the contrary, early transfusion must be instituted if prolonged ischaemia of the kidneys and probably other organs is to be avoided This is especially true after burning since the over-all peripheral resistance, that is the degree of vasoconstriction, is higher than in traumatic or haemorrhagic shock To wait for a fall of blood pressure before commencing transfusion is to court unnecessary risks A fall of blood pressure is a relatively late sign of shock and carries a bad prognostic significance It indicates first that the cerebral and coronary blood flows are reduced, and secondly either that the compensatory mechanisms are insufficient to cope with the reduced circulating volume or that they have broken down The circulation is seriously impaired, the flow of blood through the heart and brain is reduced, cerebral and cardiac anoxia may be present and death is threatened or imminent Morrison (1947) noted that the diastolic pressure might be normal or above normal for a time although the systolic pressure fell, and suggested that the reduced pulse pressure was as important as the general fall in tension

Effect of transfusion.—Practical experience has proved the value of plasma and other colloids in the treatment of burn shock Restoration of the blood volume generally reverses the circulatory failure the cardiac output and stroke volume increase the auricular and arterial pressure rise and the pulse improves For example, the cardiovascular responses to colloid therapy in a group of burned patients was reported by Hardy and his colleagues (1955) most of their patients were already hypotensive which suggested that they were in an advanced stage of shock Therapy was followed by a prompt improvement in blood pressure and cardiac output. These authors concluded that a normal cardiac output reflected adequate fluid and electrolyte therapy but this is not certain because studies of renal hepatic, skin or muscle blood flow were not made Sometimes after several days of vigorous therapy the output of the heart rose to abnormal high levels but later subsided to normal The effects of transfusion on regional blood flows and vasoconstriction needs further investigation

Irreversible shock.—Fortunately the cardiac output and blood pressure are brought to satisfactory levels when adequate solutions of electrolytes and colloids are transfused in time but if therapy is unduly delayed, or sometimes for obscure reasons, the circulatory changes may persist and be irreversible to transfusion or other therapy The blood pressure and cardiac output fail to increase or rise temporarily and fall again the pulse remains fast and feeble and death ensues. Restoration of the blood volume does not reverse the circulatory failure The condition is rare and must be distinguished from the inadequate effects of under transfusion with which it was probably confused before the large fluid requirements of extensively burned patients were appreciated

The cause of irreversibility is obscure but sometimes it may be related to vasomotor decompensation and collapse (*vide infra*) In burned dogs Page (1944) showed that after a period of heightened excitability to various vasopressive drugs, cardiovascular excitability diminished until little or no change in blood pressure occurred after an injection He postulated that the increased excitability was due to a substance in the blood stream which controlled cardiovascular sensitivity and that the terminal refractoriness was related to the disappearance of this substance On the other hand Shorr and his co-workers (see Shorr 1952) found a vasodepressive substance (V D M) of hepatic origin and due to ischaemia, in the blood of experimental animals during the later stage of shock they suggested that this agent is responsible for irreversibility

Bacterial infection has also been suggested as a causative agent Early bacterial contamination of the skin or invasion of the body was stressed by Aldrich (1933) as responsible for the early circulatory effects of "toxaemia", and more recently Fine and his co-workers (*see* Fine, 1952) have raised the importance of bacteria in the pathogenesis of irreversibility in shock If bacteria are important they are liable to have particular significance after burning because the burned skin is often contaminated with various organisms within a few hours of injury (Chapter 7)

OXYGEN TRANSPORT

The effects of the circulatory disturbance after burning on oxygen transport by the blood and on tissue respiration are of special importance The oxygen content and capacity of central venous and arterial blood in a group of 9 burned patients were analysed by Richards (1943–44) in relationship to cardiac output The percentage of reduced haemoglobin in the venous blood was greater than in normal subjects, and on the average only about 60 per cent of the haemoglobin was saturated with oxygen The absolute oxygen *content* was only slightly lowered because the haemoglobin value was increased from haemoconcentration In patients with shock from skeletal trauma and haemorrhage the loss of red cell volume resulted in a lower oxygen content of the venous blood as well as a greater percentage of reduced haemoglobin than was found in the burned patients

Taking into account the lowered cardiac output an estimate was made of the amount of arterial oxygen transported to the tissues per minute (cardiac output × oxygen content of the arterial blood) and the percentage of oxygen consumed was estimated from the oxygen consumption per minute The total oxygen transported per minute was reduced in all the shocked patients, and in the burned subjects was about 50 per cent of the basal normal The proportion of oxygen consumed was raised from the basal value of 25 per cent to a mean of 36 per cent in the burned patients and 60 per cent in those with traumatic and haemorrhagic shock The absolute oxygen consumption was not decreased compared to basal values but this may have been because the patients were not totally at rest These findings indicate that all shocked patients suffer from tissue anoxia, and this is supported by the lowered alkali reserve and increase of fixed acids in the blood, particularly the raised value of lactate, which are the products of incomplete oxidation (Chapter 17) They also suggest that tissue anoxia is less in burned patients than in those with haemorrhagic or traumatic shock

A special feature in the burned subjects was that the oxygen saturation of the arterial blood was lowered in many cases for 3–7 days, and in 12 out of 19 patients it varied from 81 per cent to 88 per cent saturation There was no clinical evidence of pneumonia and no recognizable pulmonary abnormality but Richards thought that the inhalation of hot or irritant gases may have been responsible in some cases The development of subclinical pulmonary congestive atelectasis (Chapter 19) may have also played a part The data suggested that oxygen therapy might be helpful in many burned patients

VASOMOTOR ADJUSTMENTS

These may be classified teleologically into (1) compensatory mechanisms which maintain the circulation through the heart and brain by reducing it through organs and tissues not immediately necessary for survival and (2) decompensatory phenomena which reduce or abolish the compensatory vasomotor effects

COMPENSATORY MECHANISMS

Venoconstriction.—Although the pressure within the right auricle and great veins of the thorax is reduced that of the superficial veins in the arms and legs is often within normal limits this means that there is an increased pressure gradient along the veins and indicates active venoconstriction a phenomenon directly observed in the mesentery by Abell and Page (1943)

Vasoconstriction.—The reduced skin circulation in shock is a well known phenomenon The skin particularly of the extremities, is pale and cold and strongly suggests active vasoconstriction Vasoconstriction in internal organs also occurs but its full extent is unknown The evidence suggests that regional differences occur in the body and that a selective vasoconstriction shuts off or reduces the blood supply to various organs and regions in order to maintain blood flow through the brain and heart Gesell (1919) found that after blood loss the flow of blood through the submaxillary gland was reduced proportionately more than the general blood flow One of the main organs affected is the kidney normally 20 per cent to 25 per cent of the cardiac output passes through the kidneys but renal clearance studies by Lauson Bradley and Cournand (*1944*) on 35 patients with various kinds of injury and acute haemorrhage including 2 burned subjects, showed a considerable reduction in the total renal blood flow The reduced flow was proportionately greater than the fall in cardiac output and was often only 10 per cent of normal This must have been the result of renal vasoconstriction

Bacterial infection has also been suggested as a causative agent Early bacterial contamination of the skin or invasion of the body was stressed by Aldrich (1933) as responsible for the early circulatory effects of "toxaemia", and more recently Fine and his co-workers (*see* Fine, 1952) have raised the importance of bacteria in the pathogenesis of irreversibility in shock If bacteria are important they are liable to have particular significance after burning because the burned skin is often contaminated with various organisms within a few hours of injury (Chapter 7)

OXYGEN TRANSPORT

The effects of the circulatory disturbance after burning on oxygen transport by the blood and on tissue respiration are of special importance The oxygen content and capacity of central venous and arterial blood in a group of 9 burned patients were analysed by Richards (1943–44) in relationship to cardiac output The percentage of reduced haemoglobin in the venous blood was greater than in normal subjects, and on the average only about 60 per cent of the haemoglobin was saturated with oxygen The absolute oxygen *content* was only slightly lowered because the haemoglobin value was increased from haemoconcentration In patients with shock from skeletal trauma and haemorrhage the loss of red cell volume resulted in a lower oxygen content of the venous blood as well as a greater percentage of reduced haemoglobin than was found in the burned patients

Taking into account the lowered cardiac output an estimate was made of the amount of arterial oxygen transported to the tissues per minute (cardiac output $\times$ oxygen content of the arterial blood) and the percentage of oxygen consumed was estimated from the oxygen consumption per minute The total oxygen transported per minute was reduced in all the shocked patients, and in the burned subjects was about 50 per cent of the basal normal The proportion of oxygen consumed was raised from the basal value of 25 per cent to a mean of 36 per cent in the burned patients and 60 per cent in those with traumatic and haemorrhagic shock The absolute oxygen consumption was not decreased compared to basal values but this may have been because the patients were not totally at rest These findings indicate that all shocked patients suffer from tissue anoxia, and this is supported by the lowered alkali reserve and increase of fixed acids in the blood, particularly the raised value of lactate, which are the products of incomplete oxidation (Chapter 17) They also suggest that tissue anoxia is less in burned patients than in those with haemorrhagic or traumatic shock

time in spite of considerable oligaemia indicates that central nervous mechanisms are involved

Vasoconstrictive drugs.—If vasoconstriction is a beneficial compensatory mechanism is the induction of a greater degree of vasoconstriction more beneficial to the patient? Richards (1943–44) records the results of giving a vasopressor amine to an injured shocked patient The arterial pressure and peripheral resistance rose as expected but the cardiac output and auricular pressure fell further and clinically the patient was no better With subsequent transfusion the cardiac output increased the auricular and arterial pressures rose the peripheral resistance fell and the patient recovered In extensively burned dogs infusion of the vasopressor levarterenol failed to increase the cardiac output (Gilmore 1956) Vasopressive agents are not a substitute for transfusion indeed, the increase of heart work which must follow added vasoconstriction may be deleterious

VASOMOTOR DECOMPENSATION

In shock after burning and injury the vasomotor adjustments to the circulation are strained and are likely to be upset by an unfavourable environment and other causes Cardiovascular compensation is already disturbed by the deviation of blood to the burned skin and can be further upset by pain vomiting movement posture exposure to cold or excessive heat operation or by the taking of alcohol syncope collapse or death may be precipitated In patients with latent or threatened shock the full clinical signs and symptoms of shock may rapidly develop The mechanism of decompensation is not fully understood but at least in some cases regional vasodilatation is probably important A relevant observation may be that of McMichael (1944) that the onset of syncope after acute haemorrhage in human volunteers was associated with a fall in blood pressure and plethysmographic evidence of *increased* blood flow through the muscles without a further fall in cardiac output Other factors which may be involved include loss of central control from cerebral anoxia arteriolar muscle fatigue cardiac failure acidosis, electrolyte imbalance V D M from hepatic ischaemia and ischaemia of the kidneys

Pain Although pain occurs after shallow burning it is limited in time but its duration can be important in decompensating a burned patient This has long been noted by clinicians after injury and burning and it has been said that some patients bleed to death with pain The giving of morphine as a first aid *pain-relieving* measure can be

The ratio of the systemic blood pressure to the cardiac output is a measure of total peripheral resistance, since it denotes the rate of fall of pressure per unit of flow along the blood vessels It depends mainly on the degree of vasoconstriction and to a lesser extent on the viscosity of the blood Richards (1943–44) reported that the mean total peripheral resistance was greatly increased (more than twice normal) in a group of 9 burned patients and that the rise was considerably more than in patients with injury or acute haemorrhage This was not due to haemoconcentration because the two subjects with the highest peripheral resistance had normal haematocrit values Therefore an increase of blood viscosity was probably not responsible and the increased peripheral resistance resulted mainly, if not entirely, from extreme vasoconstriction

Direct microscopic observations on the mesenteric vessels of burned dogs and cats were made by Abell and Page (1943) using an *in vivo* chamber technique Ten to ninety minutes after scalding the hind limbs, they watched the onset of a progressive narrowing of the larger and smaller arteries of the mesentery which was maximal at about 2 hours and developed before the systolic blood pressure fell The flow in the vessels diminished until there was little or no movement in the smaller arteries and veins The larger veins were also constricted but there was almost no change in the calibre of the smaller veins and capillaries The arterio-venous anastomoses narrowed shortly after burning and the flowing blood was passed into the capillary system where it was trapped The effect of capillary trapping on burn shock is considered in Chapter 11

Mechanism —The manner by which vasoconstriction is produced is uncertain, but neural or humoral or both mechanisms must be responsible Reflexes originating from the aortic arch and carotid sinuses and initiated by oligaemia may stimulate the vasomotor centre in the brain stem and then the sympathetic nervous supply of the blood vessels Alternatively adrenaline, which is known to be secreted soon after burning (Chapter 18), may be partly responsible The vasoconstrictive substance described by Page (1943) may be involved He found that the plasma of burned dogs developed vasoconstrictive properties for the isolated rabbit's ear Another humoral factor which may contribute is the vaso-excitary substance of renal origin described by Shorr, Zweifach and Furchgott (*see* Shorr, 1952) However the full explanation of vasoconstriction is likely to be complex, since it must take into account the different degrees of vasomotor activity in different regions and organs of the body This, and the fact that the arterial pressure does not fall for a

of a primary cardiac disturbance but in man central failure may be difficult to identify in the presence of oligaemia because this alters auricular pressure in the opposite direction In experimentally burned rabbits functional and histological evidence of myocardial damage have been described (Fain, 1939 Kayashima, 1940) and electrocardiographic abnormalities in man have been reported by Kayashima (1940)

In rabbits subjected to extensive scalding, Fain (1939) found morphological and electrocardiographic evidence of myocardial damage The hearts of untreated animals dying within 3 days of burning showed capillary hyperaemia and sometimes focal swelling and degeneration of myocardial fibres More definite lesions were found when the animals were kept alive longer by serum injections White striae of myocardial necrosis were often visible on the anterior cardiac surface Histologically multiple discrete foci or areas of necrosis were present in the walls of both ventricles, particularly the right and necrotic foci were separated from the normal myocardium by a narrow zone of histiocytes and undifferentiated connective tissue cells Calcification of the lesions had occurred in animals surviving 5 days or longer Electrocardiographic studies frequently showed abnormalities suggestive of a serious myocardial disturbance

In severely burned rats Prinzmetal and Bergman (1945–46) found evidence of a lowered myocardial function which they related to a disturbed coronary circulation The capillary bed of the excised hearts was widely dilated which suggested to them that the coronary circulation had been decreased below the metabolic needs of the myocardium the hearts were also unduly dilated and continued to beat for a shorter time after excision than those from unburned controls Cordier and Dessaux (1950) found that extensive burning of rats failed to reduce the glycogen content of the myocardium and thought the heart was unable to utilize its glycogen reserves The work of Page (1944) on dogs suggests that the excitability of the heart changes after burning At first there was an increased excitability to vasopressive drugs, but later the excitability decreased until the heart became refractory

These results suggest that myocardial damage after burning cannot be excluded and further investigations are needed

Hyperpotassaemia and potassium sensitivity —The possibility that rapid release of potassium from red cells after burning might produce circulatory failure was suggested by Schjerning in 1884 but in burned patients reaching hospital the plasma potassium level is either normal or only slightly raised and the levels reached would not be sufficient

important, but in badly burned patients it should be given intravenously (*see* Chapter 20) and it is not otherwise indicated

Cold and heat —Exposure to cold can also change latent into overt shock or worsen the state of a shocked patient and in cold countries this may be very important (Postnikov and Frenkel, 1949) On the other hand, active warming of the skin by hot-water bottles, electric cradles or a warm environmental temperature should be avoided, for this will dilate the skin vessels and cause blood to be deviated to the warmed skin, thus increasing the effective oligaemia Postnikov and Frenkel (1949) reported that the mortality among experimentally burned animals was considerably increased when they were kept at 37°C after burning, but heating the animals by short-wave diathermy did not have this effect The importance of ambient temperature on the survival-rate of animals subjected to limb ischaemia or injected with adenosine-triphosphate has been stressed by Tabor and Rosenthal (1947), Green and Stoner (1950) and many others The optimum temperature for survival varied somewhat with the experimental conditions but was generally about 20°–25°C The mortality rates at 37°C and below 20°C were generally much greater In clinical practice the temperature of the shock therapy room should be maintained between 20° and 25°C

Posture and movement —When the lower limbs of a lying patient are lowered below the level of the heart, blood will tend to gravitate to the periphery and the effective oligaemia to central organs will be increased Movement increases the blood flow through the muscles and produces a similar effect The established nursing practices of raising the foot of the bed and prescribing absolute rest for shocked patients are probably beneficial In patients with moderate oligaemia not only may the blood pressure be raised but there may be a significant increase in the cardiac output presumably because blood is moved centrally from the lower limbs When the oligaemia is already considerable, elevating the foot of the bed fails to increase the cardiac output presumably because there is little blood in the limbs

Alcohol —The effect of alcohol on shocked patients is most unfavourable because of its strong vasodilating action By reducing the peripheral resistance it lowers the blood pressure, and by drawing blood to the periphery it reduces the perfusion of other organs

THE HEART

The cardiac effects described above are those which follow an acutely oligaemic circulation There is no definite clinical evidence

irreversibility cannot be diagnosed until the patient fails to benefit from transfusion and is moribund

REFERENCES

Abell, R. G and Page I H (1943) *Surg Gynec Obstet* 77 348.
Aldrich, R H (1933) *New Engl J Med.*, 208, 299
Barac, G (1946) *C R Soc Biol.*, 140, 1127
Bayliss, W M., Cannon, W B., Frazer J Hooper A N and Cowell, S R (1919) In *Wound Shock and Haemorrhage* M R.C Special Report Series No 25 London.
Black D A K. (1940) *Brit med. J* 2, 693
Brown, A. (1945) In *Studies of Burns and Scalds* M R.C Special Report Series No 249
Cannon, W B (1923) *Traumatic Shock* New York Appleton and Co
Cordier D., and Dessaux, G (1950) *C R. Soc Biol Paris* 145 397
Cournand, A. Riley R. L. Bradley S E Breed, E. S Noble R. P Lauson, H. D., Gregersen, M I., and Richards, D W (1943) *Surgery* 13, 964
Dobson, E. L and Warner G F (1954) *Fed Proc* 13, 36
Fain A. (1939) *Arch. int Pharm. Ther.*, 61 172.
Fine J (1952) In *First Conference on Shock and Circulatory Homeostasis* (Ed H D Green) New York J Macey Foundation.
Gesell, R (1919) *Amer J Physiol* 47 468
Gilmore J P (1955) *U.S Naval Med. Field Res Lab.*, 6, 159
— (1956) *Ibid.*, 7 25
— and Handford, S W (1956) *J app Physiol.*, 8, 393
Grant, R T and Reeve, E. B (1951) M R.C. Special Report Series No 277
Green, N H., and Stoner H B (1950) *Biological action of the adenine nucleotides* London H K Lewis.
Hardy J D., Neeley W A Wilson, F C Lovelace J R., and Jabbour E. (1955) *Surg Gynec Obstet* 101, 94
Johnson, G S., and Blalock, A. (1931) *Arch Surg* 22, 626.
Kabat, H., and Hedin, R F (1942) *Proc. Soc exp Biol., N Y.*, 49 114
Kayashima K (1940) *Taiwan Igakkai Zasshi* 39 1190, 1206
Keeley J L., Gibson, J G and Pijoan, M (1939) *Surgery* 5, 872.
Lauson, H D Bradley S E and Cournand, A. (1944) *J clin Invest* 23 381
McMichael, J (1944) *J Amer med Ass.*, 124 275
Morrison, B (1947) *Arch. Dis Childh.* 22, 129
Noble, R P and Gregersen M I. (1946) *J clin Invest* 25 172.
Page, I H (1943) *Amer J Physiol* 139 386.
— (1944) *Ibid.*, 142, 366.
Postnikov B N., and Frenkel G L. (1949) *Khirurgia*, No 4 1
Prinzmetal M., and Bergman, H. C. (1945–46) *J Mt Sinai Hosp.*, 12, 579
Richards, D W (1943–44) *Harvey Lectures* p 217
Roos, A., Weisiger J R., and Moritz, A R. (1947) *J clin Invest* 26, 505
Rosenqvist, H. (1947) *Acta chir scand.* 95, Suppl. 124
Shorr E. (1952) In *First Conference on Shock and Circulatory Homeostasis* (Ed H D Green) New York J Macey Foundation.
Tabor I and Rosenthal, S M (1947) *Amer J Physiol.*, 149 449

to produce cardiovascular effects in normal persons (Chapter 10) On the other hand there is evidence that animals in shock may be more sensitive to potassium than normal animals so that the slight changes in burned patients might be of cardiovascular significance

A considerable acute rise of the plasma potassium could occur under special conditions and contribute to rapid death Immersion of pigs in hot water for several minutes increased the body temperature and the plasma potassium level which sometimes reached 16–19 milli-equivalents per litre (Roos Weisiger and Moritz 1947) The right auricular pressure rose, there was electrocardiographic evidence of central heart failure, and the animals died Therefore acute hyperpotassaemia might account for or contribute to the early death of some patients particularly those burned under conditions in which systemic hyperthermia is an added factor such as in a conflagration in a confined space

CLINICAL IMPLICATIONS

Fluid therapy is discussed in Chapter 10 Haemodynamic and clinical considerations indicate that shock may be divided into (1) threatened or latent shock (2) reversible shock and (3) irreversible shock

In *latent* shock the overt clinical signs of shock do not appear and the state passes off with rest and oral fluids, the condition is generally restricted to patients with less than 10 per cent of the body area burned The fluid reserves of the body and vasomotor function can compensate for the loss of fluid from the blood stream Some oligaemia and haemoconcentration may be present but they do not progress The patient's state is precarious in that vasomotor compensation may be disturbed by pain vomiting movement, change of posture, alcohol, exposure to cold excessive heating or operation and clinical shock may be precipitated Nothing should be done to the patient to produce decompensation

In *reversible* shock the established signs are sweating, pallor thirst anxiety, restlessness and a quickened heart-beat later to be followed by hypotension These are largely the effects of oligaemia and may develop in patients with burns greater than 10 per cent of the body area Transfusion of plasma or other colloids is usually considered essential to restore the blood volume and the cardiac output and reverse the other circulatory effects The condition can be worsened by pain and the other factors already enumerated

Irreversible shock is a rare phenomenon and is clinically indistinguishable from reversible shock except that the patient fails to improve with *adequate* transfusion It must be emphasized that

was divided longitudinally The difference in weight between the two sides of the body averaged 3 3 per cent of the body weight and was due to subcutaneous oedema on the burned side Since this corre sponded to an average of 57 per cent of the circulating plasma volume, he concluded that the burn oedema had produced plasma oligaemia and haemoconcentration Harkins (1934) extended this work by measuring *in vivo* the progressive increase in weight of the burned side of the animal with a tipping balance He also related the burn oedema to oligaemia because he found that the volume of blood obtained by exsanguinating the burned animals was reduced compared to that from controls (Harkins 1935)

Oligaemia and haemoconcentration.—The first reports of haemocon centration in burned patients were those of Baraduc (1862) and Tappeiner (1881) In recent years and in daily clinical practice the phenomenon has been repeatedly confirmed (for example Black 1940 Gibson and Brown 1945 Gordenko 1945 Rosenqvist 1947 Demidova, Maslennikova and Kachanova, 1949) Haematocrit values of 50–60 per cent are common within a few hours of burning and values of 70 per cent or more may be found later Calculations based on the mean normal values of corrected venous haematocrit whole body haematocrit and plasma volume for patients of different age sex, weight and height (*see* Fig. 48) indicate that the plasma volume is often reduced by 10–50 per cent or even more Plasma volume determinations by the dye method in burned patients and animals have shown that reductions of 20–50 per cent are not un common (Keeley Gibson and Pijoan, 1939 Black 1940 Noble and Gregersen 1946 Cope and Moore 1947 Davies and Topley 1956) In animals or patients with extensive burns oligaemia commences within an hour of burning because local oedema forms rapidly The oligaemia deepens and the reduced plasma volume may last several days Clinically the maximum degree of oligaemia depends mainly on the extent of burning because this largely determines the amount of fluid lost in the burn but the latter also depends on other factors (*vide infra*) In general significant oligaemia and haemoconcentration occur when the burned area exceeds 10 per cent of the body surface

Noble and Gregersen (1946) measured the plasma volumes of 21 subjects with large burns and found that the reduction at the time of admission which measured up to 50 per cent of the normal plasma volume was roughly proportional to the fraction of the body surface burned The plasma volume can be reduced by 30 per cent before marked clinical signs appear (Lee and his colleagues 1942) but further reduction is badly tolerated by the circulatory system

CHAPTER 10

BURN SHOCK: OLIGAEMIA AND THE REDISTRIBUTION OF WATER, PROTEIN AND ELECTROLYTES

EXTENSIVE burning is followed by a major redistribution of body fluids with their proteins and electrolytes and this plays the leading role in the production of burn shock The development of burn oedema may produce oligaemia, haemoconcentration, protein depletion electrolyte imbalance and tissue dehydration The understanding that burn oedema was associated with haemoconcentration and oligaemia led to the great modern advance of intravenous colloid therapy which has revolutionized the early treatment of badly burned patients

OLIGAEMIA AND BURN OEDEMA

Pathogenesis —The increased capillary permeability in burned skin may permit a rapid and continued leakage of fluid from the circulation Part may pass out of the skin as a weeping exudate, but part remains for a time in the tissue spaces and forms burn oedema This acute inflammatory reaction is discussed in Chapter 3 The fluid is rich in protein and approximates to plasma in its ionic and crystalloid content, but the sodium content of the burned area is raised above that of its water content because of an altered permeability in the cells of the injured area (*vide infra*) If the burn is large sufficient fluid may leak from the circulation to produce a plasma oligaemia with an associated haemoconcentration Oligaemia is prevented, reduced or retarded by the compensatory movement of fluid into the blood stream from the general extracellular fluid reserves of the body and this may lead to dehydration

Knowledge of the relationship of burn oedema to plasma oligaemia is largely the result of the work of Underhill and his co-workers (Underhill and his colleagues, 1923, Underhill and Fisk, 1930), Blalock (1931), Beard and Blalock (1931) and Harkins (1934, 1935) Blalock burned one-third of the surface of dogs on one side of the body and found that haemoconcentration, reflected in an average increase of haemoglobin concentration of 48 per cent, developed The animals were killed 6–24 hours later and the eviscerated carcass

The degree of plasma oligaemia is not always reflected in the degree of haemoconcentration because the latter also depends on the volume of red cells lost from the circulation at the time If this is negligible the haematocrit will rise in proportion to the falling plasma volume but if red cell loss is considerable the peripheral blood haematocrit or haemoglobin value will not be raised in proportion or may even be normal and the degree of oligaemia will be masked or its presence may not be suspected It is because plasma loss is generally much greater and occurs earlier than the main red cell loss that haemoconcentration is common in extensively burned patients (Fig. 45)

Return to normal—When the leakage from the capillaries of the burned area slows down the rate of formation of oedema falls sharply the fluid in the burned tissues is then reabsorbed into the circulation and the plasma volume increases and returns to normal during the next few days The time of onset and rate of increase of the plasma volume are complex matters and are determined by (1) the volume of the oedema and its rate of absorption which in turn are largely dependent on the extent and severity of the burn (2) the amount and quality of intravenous therapy (3) the insensible and external fluid losses (4) the fluid reserves of the body and (5) the degree of sodium and protein depletion (*vide infra*) In burned patients Elkington Wolff and Lee (1940) estimated the interval after burning at which the local capillary leak was no longer significant. By correlating the total circulating plasma protein with the amount of plasma protein transfused at various times they found that a transfusion of plasma given later than 40 hours after burning was mostly retained whilst plasma given before this largely disappeared from the circulation

As the plasma volume increases the haemoconcentration lessens the peripheral blood haematocrit and haemoglobin often fall to *subnormal* levels by about the fifth or sixth day after burning as the increasing plasma volume unmasks an earlier loss of the red cell mass (Fig. 45) It has been claimed that excessive haemodilution a false anaemia may occur during this period but this is exceptional (Davies and Topley 1956) except in patients treated with excessively large volumes of intravenous plasma

Burn oedema—The volume of the burn oedema is influenced by a number of factors, the most important of which are (1) the severity of burning, (2) the time since burning (3) the slackness of the tissues burned (4) the extent of burning, (5) external loss from weeping, (6) therapy and (7) infection

Severity and time factors—In experimental animals a relationship has been shown to exist between severity that is duration and

It should be mentioned that dye methods, like the Evans blue technique of estimating plasma volume after extensive burning, underestimate the degree of oligaemia and many of the above reports are subject to this criticism The plasma-bound dye moves into the burn exudate and the plasma-space measured is greater than the plasma volume The decrease of blood volume after burning as measured by labelling the red cells is greater than the decrease obtained by methods involving the labelling of plasma (Fogelman and Wilson, 1955) This criticism also affects the results of Gilmore

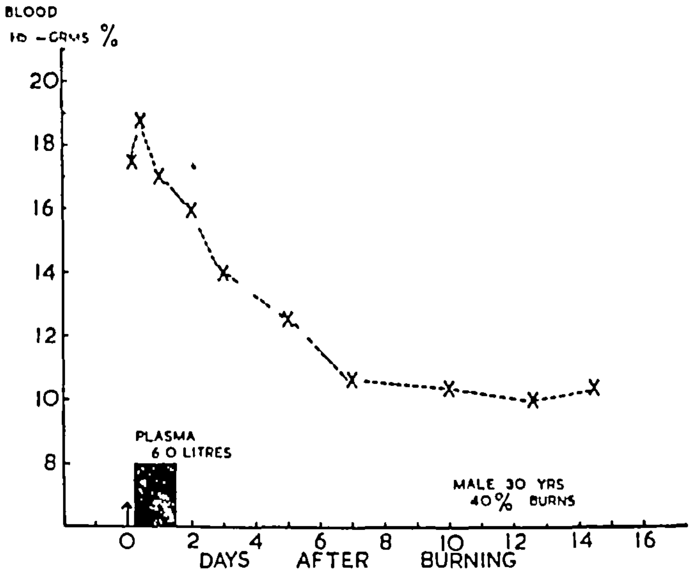


FIG 45—In this patient early haemoconcentration, the result of plasma oligaemia, was well marked When the plasma volume returned to normal the lowered red cell volume was unmasked and by the sixth day the peripheral blood was anaemic

(1955) and Gilmore and Handford (1956), who used the Evans blue technique and claimed that the initial reduction of cardiac output in burned dogs was not associated with a significant fall in plasma or blood volume

In untreated patients the duration of oligaemia is regarded as the period of burn shock and may last up to 5–6 days In adequately treated patients the duration of threatened oligaemia lasts for about 48 hours during this time the lowered circulatory volume must be combated by the administration of fluid if circulatory and renal failure are to be avoided Until this was properly understood many extensively burned patients died during the shock phase, but in recent years the frequency of death during this period has been considerably reduced (Chapter 8)

intravenous therapy has been delayed In patients under treatment with intravenous colloids the volume of the burn oedema has been shown to range from 3 to 12 litres or more and this excludes the fluid lost from the surface (Cope and Moore 1947 Hardy and his colleagues, 1955) The oedema was estimated by measuring the increase in the interstitial fluid volume by injecting sodium thiocyanate and/or radioactive sodium Cope and Moore (1947) thought that a reasonably direct relationship existed between the maximum oedema volume and the percentage area burned when this was below about 30 per cent of the body area larger burns not producing a proportionate increase in oedema However the scatter in their results and in those of Hardy and his colleagues is not inconsiderable and formulas for therapy based on their figures might lead to serious errors

Intravenous therapy —The total volume of continuously transfused plasma which is required to maintain the haematocrit or plasma volume within normal limits often greatly exceeds the whole plasma volume This means that the transfused plasma leaves the circulation for the burned skin but there is also evidence that some of the plasma water is deviated with sodium into the dehydrated and sodium depleted general interstitial space (*vide infra*) The experimental observations of Cope and Moore (1944) and Fine and Seligman (1944) showed that intravenously injected protein (labelled radioactively) rapidly entered the burn oedema Moreover the addition of large amounts of plasma to the leaking circulation of burned patients led to a greater and more rapid loss of plasma from the blood stream and increased the burn oedema (Elkington Wolff and Lee, 1940) further the volume of the burn oedema (thiocyanate space increase) of extensively burned patients was greater than the gain in body weight derived from intravenously administered colloid (Hardy and his colleagues 1955)

Thus the more colloid is transfused the more leaves the circulation and the greater the burn exudate This raises a problem in therapy On the one hand it has been claimed that overzealous transfusion could greatly and dangerously expand the extracellular space (Cope and Moore 1947 Hardy and his colleagues 1955) but on the other undertransfusion in a mistaken attempt to prevent excessive oedema will fail to correct the oligaemia The balance between excessive zeal and undertransfusion is not always easy to strike Serial haematocrit and frequent measurements of urine output are of great value in the control of transfusion therapy (*vide infra*) but the difficulty in therapy will only be solved when agents which efficiently reduce abnormal

temperature of burning, and the amount of oedema formed Within certain limits the more severe the burn the greater the rate of oedema formation, the maximum amount formed and the longer the duration of the oedema (Leach, Peters and Rossiter, 1943, Sevitt, 1954) In these experiments a series of animals were burned with a constant-temperature burning-iron for known lengths of time followed by excision of the burned skin at various intervals after burning The oedema was estimated by the wet-weight/dry-weight method The curves in Fig 19 (Chapter 3) represent the oedema in guinea-pig skin burned at 60°C for 5, 10, 30 and 60 seconds The mean maximum additions to the water content were 20, 180 250 and 260 per cent above normal respectively In the two severer burns more than two-thirds of the oedema accumulated within an hour of burning and the oedema was maximal at 4–8 hours after burning At 24–30 hours oedema was still considerable, but tests of capillary permeability at this time (by injection of Evans blue into the circulation) showed that permeability was not much increased This indicated that most of the oedema fluid had accumulated earlier The delayed increase in oedema in the 10-second burn is of theoretical interest (Chapter 3) Prinzmetal, Bergman and Hechter (1944) claimed that scalds with boiling water in rats produce relatively less oedema than scalds at lower temperatures, however, this conclusion has been disputed The variation of oedema with temperature and duration of burning is one reason why it is difficult to apply burned surface area formulas for the fluid requirements of patients, where the time-temperature severity of the burns is rarely if ever known

Slackness of tissues —The volume of the exudate also depends on the site of burning For example relatively more fluid accumulates in the slack tissues of the face, neck and scrotum than in the feet or forearm This is because the tissue pressure rises less quickly in loose than in tight skin and more fluid must accumulate before comparable pressure effects on the capillaries in the burned area can take place (Chapter 3)

Extent of burning —It is obvious that, other factors being equal, more fluid leaves the circulation and accumulates in a large burn than in a small burn and this is the basis of surface area formulas to guide colloid replacement therapy In extensive burns the volume of the oedema may be measured in litres and is often considerably more than the whole plasma volume In untreated animals this indicates that the ultimate source of much of the fluid must be the unburned tissues (Keeley, Gibson and Pijoan, 1939) This is also evident from the gross oedema which develops in extensively burned patients in whom

across capillary membranes and so commence tissue dehydration This mechanism cannot be responsible when there is no increase in the plasma protein concentration or when it falls progressively after burning, so that other processes must also occur The movement of fluid may depend on the lowering of the blood volume since it is oligaemia which is the underlying cause of the dehydration

If the burn is moderate in extent, up to 10 per cent of the body area, the transfer of fluid from other tissues may prevent or considerably reduce the oligaemia, particularly if water or saline is drunk but with burns larger than about 15 per cent of the body area neither oligaemia nor dehydration can be prevented without intravenous therapy In more extensively burned patients the extracellular fluid reserves are drained and there may be a loss of cellular water This concept is in conflict with that of certain workers who maintain that there is an increase in cellular water outside the burned area (*vide infra*) Movement of interstitial fluid into the blood continues until exudation into the burn ceases and the blood volume has returned to normal or near normal thereafter the oedema is absorbed and rehydration of the tissues occurs In those who die without fluid therapy dehydration continues until the fluid reserves are exhausted or until death occurs from circulatory failure or other causes Tissue dehydration can be considerable Measurement of the water content of tissues in poorly transfused extensively burned subjects dying within 1 or 2 days of burning has shown that the water content of muscle may fall to 50–65 per cent and in one patient the lungs contained only 30 per cent of water (Sevitt, 1949)

There is evidence that tissue dehydration may occur in patients apparently well treated with intravenous colloids Hardy and his colleagues (1955) found that the volume of the burn oedema in cubic centimetres was greater than the increase in body weight in grammes and concluded that the difference was due to a loss of water in unburned tissues In Birmingham Graber (1957) found that burned patients whose oligaemia was being or had been corrected by continuous intravenous plasma containing about 5 grammes of protein per 100 millilitres went through a phase of hyperproteinaemia and increased colloid osmotic pressure during the course of therapy This might well induce dehydration of the unburned body tissues unless the protein content of the interstitial fluid increased in proportion to that in the plasma

PLASMA PROTEINS

The fluid leaking from the capillaries in the burn has so far been considered without taking into account its protein content The

the amount lost in the exudate and that returning to the circulation *via* the lymphatics and capillaries (Chapter 3) In untreated subjects the fall in the total circulating protein is less than the total loss of protein by the amount transferred from the mobile reserves in the tissues and in treated subjects by the net gain of protein both from the mobile reserves and from plasma transfusion The plasma protein concentration is influenced by these factors and also (1) by the relatively greater loss of water than protein from the blood stream

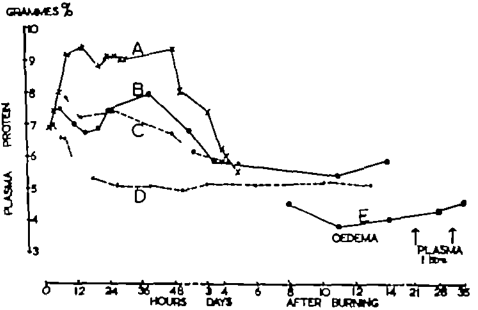


FIG 46.—Hypoproteinaemia after extensive burning and its modification by plasma therapy

Serial plasma protein concentrations in five extensively burned patients, 4 (A to D) during and after the course of resuscitation by plasma (first 36–72 hours) and one (E) later Hypoproteinaemia was delayed in onset for 48–72 hours in A, B and C whilst it developed during the first 12 hours in D A phase of hyperproteinaemia most pronounced in A occurred in the first 3 patients (*see* text) The severe hypoproteinaemia in case E was a relatively late phenomenon, was associated with extensive sloughing and granulating burns and was deep enough to cause some generalized oedema.

Curves A to C by courtesy of Dr O Graber)

into the exudate (2) by the increased loss of body water partly from increased evaporation from the burned surface particularly when the burn is moist (3) by the degree of haemodilution due to absorption of water from unburned tissues which in turn depends on the state of hydration of the patient and other factors and (4) by the relative amounts of plasma protein and non-colloid fluid administered therapeutically their route of administration and rate of absorption In this complex situation the plasma proteins are in a state of dynamic

exudate is rich in protein containing 30–60 grammes per litre, therefore the total loss is considerable when burning is extensive. The *total* amount of circulating protein falls (plasma volume multiplied by protein concentration) and a reduction in its *concentration* follows because the blood is diluted with protein-poor fluid absorbed from the tissues. Tissue fluid contains only about 1 or 2 grammes of protein per 100 millilitres. Loss of water from the plasma is relatively greater than that of protein and this delays the onset of hypoproteinaemia and occasionally results in an episode of slight hyperproteinaemia which precedes the fall in the protein level. During this phase the normal or raised plasma protein concentration is associated with a reduction in total circulating protein because of the plasma oligaemia. The loss of albumin into the exudate is often relatively greater than the loss of globulin, presumably because of its smaller molecular size, and this selective loss leads to a greater reduction in the plasma albumin level and a fall in the albumin to globulin ratio.

The changes in the plasma protein level and hypoproteinaemia in patients have been noted or studied by Davidson and Matthew (1927), McIver (1933), Weiner, Rowlette and Elman (1936), Lombard and Montpellier (1937), Black (1940), Elkington, Wolff and Lee (1940), Taylor and his colleagues (1943), Anderson and Semeonoff (1945), Cope and Moore (1947), Keyser (1948), Gefter and Miluiskevitch (1949), Graber (1957) and others, whilst in experimental animals observations have been made by Simonart (1930), Schievers (1936), Trusler, Egbert and Williams (1939), Keeley, Gibson and Pijoan (1939), Lischer, Elman and Davey (1944), Clark, Peters and Rossiter (1945), Courtice (1946), Cope and his colleagues (1948) and Brooks and his colleagues (1951). The findings indicate that hypoproteinaemia may not only develop during the early exudative phase but may also be found or develop at a later stage, particularly in patients with extensive full thickness skin-loss burns which slough and ooze. It is therefore convenient to distinguish (1) early hypoproteinaemia and (2) later hypoproteinaemia, while recognizing that the former may merge into the latter. Both are considerably influenced by plasma therapy which prevents or reduces the degree of hypoproteinaemia.

Early hypoproteinaemia.—As already noted, in extensively burned subjects there is a considerable reduction in the total circulating protein and this is often associated with or leads to a fall in the protein concentration. The total amount of protein *lost* depends on the rate and duration of loss into the burn, which in turn largely depend on the extent and severity of burning. It is a balance between

protein levels usually returned by the second week in those more extensively burned the plasma protein concentration was generally lower and the hypoproteinaemia more prolonged In patients with large burns Black (1940) noted that the plasma protein fell to 3 8–5 8 grammes per 100 millilitres in different patients Similar results were also reported by Gefter and Miluiskevitch (1949) who studied the plasma protein concentrations in 175 burned patients in Leningrad The plasma protein level often fell to 5 or 6 grammes per 100 millilitres and was sometimes 4 grammes per 100 millilitres or less when the burns involved 30–50 per cent of the body area

Gefter and Miluiskevitch (1949) also found that the hypoproteinaemia was influenced by the patient s previous nutritional state Those burned soon after the end of the war whose rations had been very limited for years because of the siege conditions in Leningrad developed a deeper and more prolonged hypoproteinaemia than those burned during the following years and living on a better diet. This experience means that the loss of protein after burning depletes the mobile reserves of body protein and that when these are already low before burning the further depletion produces a deeper and more prolonged hypoproteinaemia This is supported by the observations on untreated burned dogs by Keeley Gibson and Pijoan (1939) who calculated that the amount of protein lost into the burn was much greater than the amount lost from the plasma The difference was a loss of rapidly mobilizable body protein

The lowered concentration rises and may return to normal during the next few days presumably because protein rich oedema fluid is reabsorbed into the circulation Restoration may be delayed for weeks when the surface losses of protein have been considerable or when there is a continued drain of protein from the surface of large unhealed burns Restoration finally depends on the net loss of protein in the early exudate on the adequacy of plasma protein therapy on the protein reserves of the patient, on continued surface losses, on protein katabolism and possibly on liver function Low levels can always be raised by plasma or blood transfusion but in many patients the degree of hypoproteinaemia is only modified This is probably because the total (that is plasma plus tissue) depletion is underestimated and insufficient protein is transfused

Influence of fluid therapy—The protein level is influenced by the nature and amount of fluid therapy When burning is extensive there is a relatively steep fall during the course of or at the end of resuscitation treatment and this may or may not be preceded by a period of a raised or normal protein level (Fig. 46) The course of development

lack of equilibrium, the total amount circulating and the relative concentrations of albumin and globulin in the plasma react to the large burn wound and to the manner of treatment, influencing and influenced by the mobile reserves of protein and the state of hydration of the unburned tissues.

The investigations of plasma protein changes have been made by studying the plasma protein levels at various intervals after burning. In untreated experimental animals burning is followed by a rapid fall in the plasma protein level. This begins within an hour or two of burning, progresses during the subsequent 4–12 hours and reaches a level of 70–85 per cent of the pre-burn value (Clark, Peters and Rossiter 1945, Courtice, 1946, Brooks and his colleagues 1951). The lowered concentration is maintained for a variable period, but by 24–72 hours after burning the level has increased and may be returning to normal. Clark and his colleagues (1945) scalded the posterior third of rabbits and 4 hours later the plasma protein concentration had fallen to between 70 per cent and 85 per cent of the pre-burn values, three days later the protein levels were returning to normal. Scalding of rats was followed by a lesser fall and the protein concentration had returned to normal by 24 hours. Courtice (1946) made serial plasma protein observations during the first 6 hours after scalding both hind limbs of rabbits. A steep fall in the plasma protein level was found at 1 hour, thereafter the rate of fall was less steep and the lowest concentrations were observed at 6 hours. By 24 hours the plasma protein level was rising. A similar series of changes was observed by Brooks and his colleagues (1951) after inflicting burns at 60°C for 1 minute on 20 per cent of the body area of dogs. A fall in the protein level of the plasma had occurred by 2 hours, the maximum fall of about 20 per cent lasted from 12–24 hours and by 48 hours after burning the plasma protein concentration had increased. It is noteworthy that Courtice (1946), Lischer, Elman and Davey (1944) and Brooks and his colleagues (1951) found that haemoconcentration and hypoproteinaemia developed simultaneously. Their findings indicate that the loss of fluid into the burn and gain of fluid from the general body tissues occur simultaneously since haemoconcentration is due to loss of plasma water and hypoproteinaemia to dilution of plasma protein.

The level and duration of the hypoproteinaemia depend on the extent of burning. Anderson and Semeonoff (1945) found that patients with burns involving less than 5 per cent of the body area showed little or no fall in the plasma protein level, those with burns ranging from 6 per cent to 15 per cent of the body area often had a fall of plasma protein to 5 or 6 grammes per 100 millilitres, but normal

protein levels usually returned by the second week in those more extensively burned the plasma protein concentration was generally lower and the hypoproteinaemia more prolonged In patients with large burns Black (1940) noted that the plasma protein fell to 3 8–5 8 grammes per 100 millilitres in different patients Similar results were also reported by Gefter and Miluiskevitch (1949) who studied the plasma protein concentrations in 175 burned patients in Leningrad The plasma protein level often fell to 5 or 6 grammes per 100 millilitres and was sometimes 4 grammes per 100 millilitres or less when the burns involved 30–50 per cent of the body area

Gefter and Miluiskevitch (1949) also found that the hypoproteinaemia was influenced by the patient's previous nutritional state Those burned soon after the end of the war whose rations had been very limited for years because of the siege conditions in Leningrad developed a deeper and more prolonged hypoproteinaemia than those burned during the following years and living on a better diet This experience means that the loss of protein after burning depletes the mobile reserves of body protein and that when these are already low before burning the further depletion produces a deeper and more prolonged hypoproteinaemia. This is supported by the observations on untreated burned dogs by Keeley Gibson and Pijoan (1939) who calculated that the amount of protein lost into the burn was much greater than the amount lost from the plasma The difference was a loss of rapidly mobilizable body protein

The lowered concentration rises and may return to normal during the next few days presumably because protein rich oedema fluid is reabsorbed into the circulation Restoration may be delayed for weeks when the surface losses of protein have been considerable or when there is a continued drain of protein from the surface of large unhealed burns Restoration finally depends on the net loss of protein in the early exudate on the adequacy of plasma protein therapy on the protein reserves of the patient, on continued surface losses on protein katabolism and possibly on liver function Low levels can always be raised by plasma or blood transfusion but in many patients the degree of hypoproteinaemia is only modified This is probably because the total (that is plasma plus tissue) depletion is underestimated and insufficient protein is transfused

Influence of fluid therapy—The protein level is influenced by the nature and amount of fluid therapy When burning is extensive there is a relatively steep fall during the course of or at the end of resuscitation treatment and this may or may not be preceded by a period of a raised or normal protein level (Fig 46) The course of development

of hypoproteinaemia depends on the relative amounts of plasma and non-colloid fluid given A steady fall in the plasma protein concentration occurs when little plasma protein is administered and when treatment is mainly by non-colloids like saline given orally or intravenously With such therapy haemodilution will be hastened, the proteins lost into the burn are not replaced, and a rapid and perhaps considerable fall in the plasma protein concentration will appear This may also occur when both plasma and saline are given intravenously in about equal amounts, since the rate of gain of protein in the plasma may not balance the rate of protein loss The development of hypoproteinaemia in many treated patients such as those reported by Cope and Moore (1947) can be explained on this basis They transfused patients with considerable but equal quantities of plasma and saline, gave additional fluids by mouth and reported the development of hypoproteinaemia

When treatment is mainly by reconstituted plasma, which in Britain contains about 5 grammes of protein per 100 millilitres, and when non-colloid fluid is given in limited amounts the time of appearance of hypoproteinaemia will depend on the rate and adequacy of transfusion If transfusion is inadequate oligaemia will not be corrected, the total circulating protein will fall, protein-poor interstitial fluid will be absorbed into the blood stream from unburned tissues and hypoproteinaemia will be found by 12–24 hours after burning Oral fluid therapy hastens haemodilution and increases the rate of fall of the protein level in the plasma, whilst the increased loss of water from the body surface sustains oligaemia, retards haemodilution and the appearance of the fall in the protein concentration On the other hand if plasma is given so that the blood volume is rapidly restored to normal or near to normal and maintained during the period of resuscitation, the fall in the plasma protein concentration is delayed until after resuscitation therapy has ceased, that is for about 2–3 days

During the course of such therapy the plasma protein concentration usually rises and may reach a level of 8 or 9 grammes per 100 millilitres (Graber, 1957) This must be either because the rate of administration of protein from a few hours after burning and onset of therapy is greater than the net rate of loss into the burn during this period, or because a higher rate of transfusion of plasma water is required to balance the total loss of water from the blood stream, or for both reasons The lost water consists not only of exudate and urine but also of sensible and insensible losses from the skin and lungs, and these may be greatly increased The balance of evidence suggests that it is the increased surface losses of water which mainly

account for the phase of hyperproteinaemia because the concentration of protein in reconstituted plasma is about equal to that in burn exudate but further investigations are necessary This phase of hyperproteinaemia which is induced by therapy is to be distinguished from that reported by Cope and his colleagues (1948) which was said to occur before therapy had begun Therapy induced hyper proteinaemia is associated with a raised total circulating plasma protein because the plasma volume is normal or nearly normal whilst spontaneous hyperproteinaemia would be associated with a reduction in the total circulating protein and with a definite plasma oligaemia

The finding of therapy induced hyperproteinaemia may have certain lessons Although during the first few hours of resuscitation adequate transfusion of plasma containing 5 grammes of protein per 100 millilitres rapidly restores the total circulating protein and the plasma volume to normal continued transfusion of the plasma at the rate necessary to prevent oligaemia may lead to a phase of hyper proteinaemia This may mean either that the concentration of protein in the transfusion fluid should be reduced after a few hours or that non-colloid fluid should be pressed orally The consequences of hyper proteinaemia may be serious tissue dehydration (clinically manifested by thirst) and a reduction in glomerular filtration may be precipitated

Albumin and globulin —The fall in the total protein concentration of the plasma is associated with a greater decrease in the albumin than in the globulin fraction and is associated with a lowered albumin globulin (A G) ratio This is partly explained by a selective loss of albumin and a lesser loss of globulin into the burn exudate because of the lower molecular size of the former and because some differential permeability is retained by many capillaries in the burn In experimental animals the selective fall of the plasma albumin and the reduced A G ratio were described by Lischer Elman and Davey (1944) Clark, Peters and Rossiter (1945) and others The preferential escape of albumin compared to globulin in burn oedema of rabbits was first noted by Underhill and Fisk (1930) and was studied in the lymph draining from a burned area by Cope and Moore (1944) Analysis of blister fluid removed within a day or so after burning has shown that whilst its total protein content ranges from 60 per cent to 80 per cent of that in the plasma its albumin level may be 80–90 per cent and its globulin level only 40–70 per cent of the respective plasma levels (Presman and his colleagues 1943 Abbott and his colleagues 1945 Cope and his colleagues 1948) The A G ratio of early bleb fluid is generally higher than that in the plasma It is uncertain whether blister fluid is representative of the exudate

in burned skin and serial studies of the total protein, albumin and globulin contents of subcutaneous oedema are needed

Differential escape of albumin is not the full explanation for the lowered plasma A G ratio because the absolute plasma globulin level may rise, suggesting that new globulin has been added This was first observed in patients by Davidson and Matthew (1927), who also observed a rise in the plasma fibrinogen, and has been confirmed experimentally by Lischer, Elman and Davey (1944) and Clark, Peters and Rossiter (1945) Lischer and his colleagues observed that whilst the plasma globulin level fell in relatively less severely burned dogs it rose in animals subjected to more severe burning and particularly in those who died, whilst the work of Clark and his colleagues (1945) showed that the low plasma albumin level persisted for some days whilst the globulin level progressively increased and rose above its pre-burn value

Electrophoretic studies have not only confirmed the lowered albumin and increased globulin values but have shown that the globulin increase may be concentrated in one or other fractions (Gjessing and Chanutin, 1947, Prendergast, Fenichel and Daly, 1952) Sometimes the fibrinogen and gamma globulin fractions are particularly increased and sometimes the concentration of the alpha and/or beta fractions is particularly raised An increase in fibrinogen is presumably related to liver function whilst the increase in the other globulins may be related, in part, to the lympholytic effect of adrenocortical hyperactivity (Chapters 16 and 18) This is because globulin may be released when lymphocytes are destroyed

Spontaneous hyperproteinaemia —Since the total protein concentration in the exudate is usually less than the plasma protein level it has been postulated that the initial exudation into the burn produces or rather leaves a circulating plasma with a *raised* protein concentration and colloid osmotic pressure and that this precedes the fall in the protein level (Cope and his colleagues, 1948) As already noted the concept was developed to explain the withdrawal of fluid from unburned tissues Cope and his colleagues claim to have demonstrated a transient rise in the plasma protein level of untreated burned dogs and patients, but the serial observations by other workers did not show a phase of hyperproteinaemia (Lischer, Elman and Davey, 1944, Clark, Peters and Rossiter, 1945, Courtice, 1946, Brooks and his colleagues, 1951) In their experience the plasma protein concentration fell without a transient rise in its level and this has also been confirmed by the author in burned rabbits

The early co-existence of haemoconcentration and hypoprotein-

aemia (*vide supra*) indicates that oligaemia and dehydration develop simultaneously and that the entry of protein poor tissue fluid into the blood stream counteracts the initial theoretical tendency to hyper proteinaemia The actual protein level of the plasma at any moment depends on the balance between the losses and gains of water and protein The rates of gain of water and protein will vary and will depend on the state of hydration and the protein reserves of the patient as well as the extent of burning and the rate of onset of olig aemia. These variables will influence the rate of onset of hypoproteinaemia.

Later hypoproteinaemia.—Sometimes the early hypoproteinaemia continues for weeks, whilst in other patients the early fall may be slight and there is a later fall in the plasma protein level (Fig 46) This is mainly because of a continued drain of plasma from the burned surface, particularly in patients with large whole skin loss burns This phase of hypoproteinaemia is apt to develop when the burn is sloughing and granulating and particularly when it is in fected and oozes considerably Although a continued surface loss of protein probably plays the major aetiological role, liver dysfunction and excessive protein katabolism are also said to play a part in producing hypoproteinaemia Occasionally the fall of the plasma protein is to oedema levels and in such patients energetic therapy with concentrated albumin or plasma is required this aspect of the problem was stressed by Taylor and his colleagues (1943) The low protein level may continue for weeks and until the burns are healed by grafting or otherwise Skin healing is said to be hindered by hypoproteinaemia

REDISTRIBUTION OF ELECTROLYTES

The importance of electrolyte imbalance in burn shock stems from the key observation of Davidson (1926) that a progressive fall in the plasma chloride level in burned patients was associated with a gross reduction in the urinary excretion of chloride this author therefore advocated therapy with saline In outline the electrolyte disturbance after burning is due to (1) an exudation of sodium, chloride and other ions into the local oedema together with the water protein and other constituents of the plasma, (2) a gain of sodium by the burn dis proportionately greater than the gain of water (3) a loss of potassium from the burn and (4) altered electrolyte distribution from the general reaction to injury and related to adreno-cortical hyper activity (Chapter 18) These are responsible for the lowered plasma concentrations of sodium and chloride and for the slight rise of the potassium level in many patients

Plasma electrolytes—The changes in plasma electrolytes may be taken by and large as representing those in the whole extracellular water space of which the plasma is but a part

Sodium and chloride—Within a few hours of burning the plasma sodium and chloride levels of untreated patients begin to fall and they diminish progressively for a few days when the burn is extensive Davidson (1926) was the first to note that the degree of chloride reduction was related to the extent of burning After a few days the low plasma levels rise and return to normal as sodium and chloride are absorbed from the burn oedema There is some evidence that the fall in the plasma sodium and chloride is accompanied by a rise in the sodium content of the red cells (Lowdon and his colleagues, 1939) and this may result from the movement of sodium and chloride across the cell membrane of erythrocytes injured by heat during the course of the burning The degree of fall is also influenced by the previous state of hydration of the patient and in particular by the adequacy of plasma and saline administration These variables account for some of the discrepancies in the literature In experimental animals Underhill, Fisk and Kapsinow (1930) found that haemoconcentration after burning was associated with hypochloraemia but that if haemoconcentration was avoided by transfusion there was no appreciable fall in the chloride More significantly Tenery (1941) showed that saline therapy reduced the fall in the plasma chloride The fall in plasma sodium and chloride is only modified by therapy, and even when the intake of sodium chloride is relatively high and plasma therapy is apparently adequate there is still some fall in the sodium level about the second to the fourth day (Bull and England, 1954) In treated patients the sodium fall is slight or moderate and the level rarely falls below 300 milligrams per 100 millilitres (130 milli-equivalents per litre)

Potassium and phosphate—Theoretically there is an early tendency for the potassium level to rise because this intracellular ion is released from damaged cells in the burned skin (*vide infra*) and during the course of intravascular haemolysis A significant hyperpotassaemia does not occur because the total potassium liberated is not considerable even in patients with extensive burns and because the liberated ions are freely excreted in the urine In clinical practice the plasma potassium is often within normal limits or only slightly raised, even in patients with large burns, and rarely exceeds 5 or 6 milli-equivalents per litre (20–24 milligrams per 100 millilitres) in the absence of renal failure (Wilson and Stewart, 1939, Black, 1940, Tenery, 1941, Anderson and Semeonoff, 1945, Bull and England, 1954)

In a few patients a significant *hypo*-potassaemia develops, the level falling to about 3 milli-equivalents per litre sometimes this is associated with diarrhoea but often its cause is obscure Inadequate intake in the face of a free urinary excretion may contribute

The serum inorganic phosphate is often raised in patients (Green and his colleagues, 1949) This is partly related to the liberation of potassium and partly to the disturbances in carbohydrate and protein metabolism (Chapter 17)

Bicarbonate —The post burn tendency to acidaemia which partly results from the sudden but temporary increase in the lactic acid content of the blood produces a fall in the plasma bicarbonate

Changes in the burn.—The relationship of the sodium level in the serum to the changes in the arterial and venous blood in the burned area was studied by Lowdon and his colleagues (1939) The serum of the venous blood from the scalded skin of cats contained less sodium than the serum of the arterial blood and the serum sodium level in the general circulation fell This indicates that the loss of sodium into the burn is greater than the loss of water This conclusion was confirmed by perfusing the isolated hindquarters of the cat with heparinized blood at one hour after burning a sharp fall in the plasma sodium was observed and the outflow plasma contained less sodium than the inflow plasma Quantitative estimates of the tissue water and electrolyte content of the scalded hind limbs of mice were reported by Fox and Baer (1947) who found that the gain of sodium by the limb was in excess of water that potassium was lost and that the excess of sodium was equivalent to the lost potassium The excessive uptake of sodium confirmed the previous work (Fox and Keston 1945) in which radioactive sodium was used as a tracer to compare the sodium content of normal burned and tourniquet injured tissue Similar results were reported by Tabor and Rosenthal (1945) for the limbs of mice subjected to tourniquet trauma The results indicate an equimolecular exchange of sodium and potassium ions between the extracellular fluid in the burn and the injured tissue cells in addition to the exudation of a plasma like exudate into the burned area This exchange of potassium for sodium in burned skin which was confirmed by Moore, Evans and Ball (1948) is not restricted to heat-affected tissue and appears to be a regular accompaniment of many kinds of injury and is possibly related to a disturbance of the vital activity of the cell membrane (Chapter 2)

Changes in unburned tissues.—In the tourniquet experiments of Fox and Baer (1947) the sodium and potassium contents of the

opposite uninjured limb were also estimated and the results compared with those of normal controls A slight but significant decrease in the total sodium of the uninjured limb was associated with a similar increase in its potassium content These results are in agreement with those which would be expected from the sodium and potassium levels of the plasma since the latter represent the whole extracellular fluid

Significance.—The majority of workers believe that the prime mover in the pathogenesis of burn shock is the deviation of water, protein and electrolytes into the burn, resulting in a plasma oligaemia or "white bleeding" On the other hand a minority consider that this concept is unsatisfactory (Rosenthal, 1943, Fox, 1944, Rosenthal and Tabor, 1945, Fox and Baer, 1947) They argue that since the sodium content of the extracellular fluid is lowered by the excessive deviation of sodium into the burn, the interstitial osmotic pressure is lowered Water must then move from the general interstitial space into uninjured cells just as red cells imbibe water and swell when placed in hypotonic solution This would dehydrate the sodium-depleted extracellular fluid compartment, and since the plasma is a part of this, its volume would be lowered The results of Fogelman and Wilson (1955) would appear to support the concept of intracellular dehydration but are subject to criticism They found that the total body water of burned dogs and man remained unaltered whilst there was a *decrease* in the extracellular space as measured with radioactive sulphur This is in conflict with other workers (Cope and Moore, 1947, Hardy and his colleagues, 1955) who found that the interstitial fluid volume was considerably increased as measured after injecting sodium thiocyanate or radioactive sodium An unusual slow exchange of the injected substance between plasma and burn exudate may have been responsible for the results of Fogelman and Wilson Nevertheless the possibility that intracellular over-hydration occurs in certain circumstances cannot be excluded

Potassium sensitivity—It is agreed that the rise in plasma potassium after burning is insufficient to cause clinical effects in normal subjects except under special conditions (Chapter 9), but it has been suggested that the tissues of shocked individuals are more sensitive to potassium and that the total potassium released is sufficient to cause toxic effects (Rosenthal and Tabor, 1945, Tabor and Rosenthal, 1945) They found that when potassium chloride was administered to shocked mice its minimum lethal dose was only about one-tenth of that for normal animals although the lethal doses of

magnesium and quinidine were less than halved Moreover when rabbits subjected to tourniquet shock were killed by intraperitoneal injection of potassium chloride the serum potassium levels found were similar to those of rabbits not given potassium chloride

An excessive sensitivity of burned patients to normal or slightly raised plasma potassium levels should be detectable electrocardiographically and this is being investigated in Birmingham

Therapeutic significance.—All workers agree that since sodium and chloride move with water into the burn sodium therapy is necessary Most maintain that plasma is the fluid of choice and that its electrolytes are either sufficient to balance the loss into the oedema or that additional sodium as chloride or lactate is desirable whilst a minority insist that large amounts of saline are essential and that colloid therapy is not necessary The problem has not been settled but in clinical practice there does not appear to be a hard and fast rule about the amount of saline required, because similar therapeutic results can be obtained with low and high intakes of sodium provided that plasma therapy is adequate At one period in Birmingham the dried plasma for transfusion was dissolved in normal saline thus doubling its sodium content, and sodium lactate was given by mouth but the results were no better than those obtained by the administration of water-dissolved plasma

The schools of Rosenthal and Fox advocate the administration of large volumes of saline 10–15 per cent of the body weight, by any route Rosenthal (1943) found that the mortality in mice within 48 hours of burning was greatly reduced when sodium salts were administered The administration of plasma was no more effective than saline plasma was as effective orally as intravenously and its effectiveness resulted from its sodium content all sodium salts had beneficial effects and potassium salts antagonized the beneficial effects of sodium (Tabor Kabat and Rosenthal 1944 Tabor and Rosenthal 1945) The acute survival rates after different kinds of treatment were compared with certain indices of haemodynamic function found after therapy (bleeding volume haematocrit and plasma protein concentration) and these were not closely related to the ability to survive for 48 hours (Millican and his colleagues, 1952) Restoration of the haemodynamic indices to normal was related to transfusion of colloids like plasma or albumin solution but survival was mainly related to multiple dose therapy and the volume of fluid administered when it contained isotonic sodium Saline therapy was highly effective given orally or parenterally in a volume corresponding to 10–15 per cent of the body weight This was confirmed

by Moyer and his colleagues (1944) who found that saline-bicarbonate or Ringer-lactate solution was more effective than isotonic saline, similar conclusions were reached by Hechter, Bergman and Prinzmetal (1945)

In man, sodium therapy was advocated by Fox (1944) who successfully treated a group of burned patients with oral sodium lactate A controlled clinical trial on 193 extensively burned patients was made by Markley and his colleagues (1956) in Peru Alternative patients were given large doses of saline (15–17 per cent of the body weight) during the first 2 days orally or intravenously or by both routes The others were treated by continuous intravenous therapy with plasma, blood or polyvinylpyrrolidine (2 4–3 2 per cent of the body weight) supplemented by glucose or sucrose solution but without additional sodium There was no difference in the over-all or 48-hour mortality between the groups, although the actual mortalities in both groups, particularly among the children, were relatively high The large volumes of saline were said to have been well tolerated although the burned areas must have been grossly distended Apparently neither generalized nor pulmonary oedema occurred

The reasons given by the advocates of massive saline therapy are not necessarily those responsible for its effectiveness It is possible that the therapy works by increasing the tissue pressure The gross and progressive swelling of the burned area during the therapy must increase the tension within the tissues and, if this rises above the capillary pressure, exudation must cease

FLUID THERAPY

The question of massive saline therapy has already been discussed and this section is restricted to the usual forms of colloid therapy

The aim of fluid therapy is to save life by (1) restoring and maintaining the plasma and red cell volume, (2) correcting or preventing dehydration and (3) restoring the plasma proteins and electrolytes lost temporarily or permanently in the exudate

Continuous intravenous therapy of a colloid is necessary when the burn is greater than 10–15 per cent of the body area and additional oral fluid should be given when the absence of vomiting permits

Human plasma is the fluid of choice to restore the lost protein Non-protein colloids such as 6 per cent dextran in saline and polyvinylpyrrolidine have been used with success (Rosenqvist, 1947, Bull and colleagues, 1949, Markley and colleagues, 1956) Owing to the increased danger of plasma protein depletion the volumes given should be restricted to less than the patient's plasma volume and further transfusion should be with whole blood or plasma Harkins

(1954) recommends restricting the volume of dextran to less than 1 litre per day because of its haemorrhagic inducing tendency The long term results of dextran therapy need to be studied before it is recommended since there is evidence of dextran storage in tissues for months or years after administration

Additional salt and water are required to replace physiological losses and glucose should be given for energy requirements Whole blood should also be transfused to replace lost red cell mass

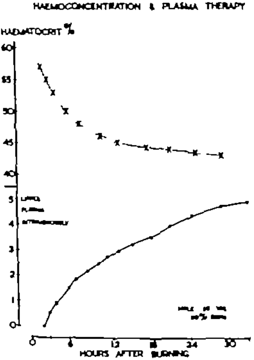


Fig 47 —Control of plasma therapy by serial haematocrit observations. The volume of plasma indicated is cumulative.

and thereby combat red cell oligaemia and anaemia (Chapter 15) Some clinicians advocate the use of whole blood without plasma and Moyer (1953) recommends intravenous buffered saline and whole blood

Relatively more fluid has to be transfused during the first 8–12 hours because exudation into the burn is greatest during this period The rate of transfusion must take into account the fluid already lost as well as the current rate of loss Intravenous therapy must continue for at least 24 and up to 48 hours or occasionally longer that is until exudation is judged to have ceased or until oral fluids alone will suffice to maintain a normal blood volume Under transfusion and

over-transfusion should be avoided The former allows oligaemia to continue with its dangers of circulatory and renal failure, whilst the latter might produce pulmonary oedema from early overloading of the circulation or a generalized oedema (in addition to pulmonary oedema) during reabsorption of the burn exudate if the renal excretion of water is inadequate

Repeated clinical examination is essential and the most useful symptoms of oligaemia and insufficient therapy are thirst, restlessness and cold extremities A fall in blood pressure is a late sign and may have serious consequences

Many formulas have been recommended to estimate the amount of plasma required but these are of doubtful value As a rough guide Bull and Jackson (1952) make the simple recommendation that adults require a total of 1–1½ litres of plasma during the first 24 hours for every 10 per cent of the body surface burned Half of this should be given during the first 8 hours The plasma requirements of burned children are so variable that no formula can really forecast them, but roughly 1 plasma volume of the child is required during the first 24 hours for every 15 per cent of the body area burned

The rate and volume of transfusion should be guided by (1) serial estimates of the peripheral haemoglobin or haematocrit (Fig 47) and (2) the rate of flow of urine

(1) *Serial haematocrit estimates* are preferable to haemoglobin determinations because they can be performed accurately by the clinician in a ward side room if an electrically driven centrifuge is available At first the observations should be made hourly, later, 2-hourly or 4-hourly estimates will suffice Capillary blood from an unburned area may be transferred by a dry heparinized pipette to a small heparinized test-tube and thence to the narrow-gauge Meyerstein haematocrit tube which requires less blood than the Wintrobe tube with its wider bore

The estimated haematocrit is corrected for trapped plasma (*see* legend, Fig 48) and the corrected value is compared with that of the mean normal venous haematocrit for the patient's age, weight or preferably height from a chart of mean normal values (Fig 48) This chart also includes the mean normal values for the whole body haematocrit, plasma volume and red cell volume Assuming that the red cell volume has remained unchanged the patient's plasma volume can be calculated and the deficit in the volume, that is the degree of oligaemia, assessed The rate of loss of plasma from the circulation (in millilitres per hour) is estimated from the number of hours since burning if this was recent The rate of transfusion is adjusted according to the calculated deficit in the plasma volume, the

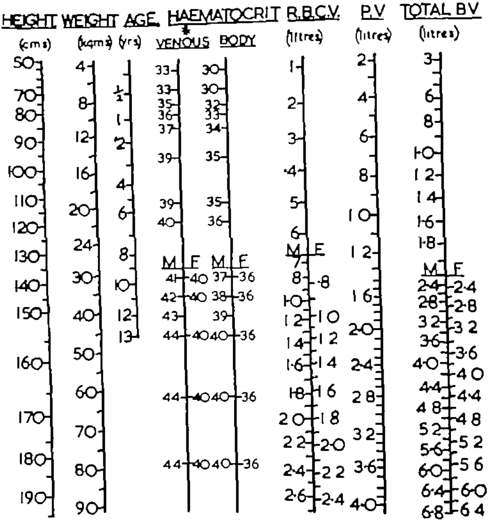


FIG 48 —Mean normal values of total blood volume (B V) red cell volume (R.B C.V) plasma volume (P V) and haematocrit corresponding to various heights, weights and ages and for both sexes. Height is the most reliable criterion (*After Topley and Jackson* 1957)

NOTE. (1) The venous haematocrit values given have been corrected for trapped plasma and are 5–10 per cent lower than those found after 30 minutes centrifugation at 3 000 revolutions in most laboratory centrifuges. In practice, when the centrifuge haematocrit readings are between 20–30 31–50 and 51–71 per cent, the corrected venous haematocrits may be calculated by subtracting 2, 3 or 4 respectively

(2) The whole body haematocrit $\left(\frac{\text{R.B.C V}}{\text{Total B V}}\right)$ is about 90 per cent of the venous haematocrit in both normal and burned patients and for convenience is included in the chart. (*By courtesy of Dr E. Topley and the Editor of J clin Path*)

over-transfusion should be avoided The former allows oligaemia to continue with its dangers of circulatory and renal failure, whilst the latter might produce pulmonary oedema from early overloading of the circulation or a generalized oedema (in addition to pulmonary oedema) during reabsorption of the burn exudate if the renal excretion of water is inadequate

Repeated clinical examination is essential and the most useful symptoms of oligaemia and insufficient therapy are thirst, restlessness and cold extremities A fall in blood pressure is a late sign and may have serious consequences

Many formulas have been recommended to estimate the amount of plasma required but these are of doubtful value As a rough guide Bull and Jackson (1952) make the simple recommendation that adults require a total of 1–1½ litres of plasma during the first 24 hours for every 10 per cent of the body surface burned Half of this should be given during the first 8 hours The plasma requirements of burned children are so variable that no formula can really forecast them, but roughly 1 plasma volume of the child is required during the first 24 hours for every 15 per cent of the body area burned

The rate and volume of transfusion should be guided by (1) serial estimates of the peripheral haemoglobin or haematocrit (Fig 47) and (2) the rate of flow of urine

(1) *Serial haematocrit estimates* are preferable to haemoglobin determinations because they can be performed accurately by the clinician in a ward side room if an electrically driven centrifuge is available At first the observations should be made hourly, later, 2-hourly or 4-hourly estimates will suffice Capillary blood from an unburned area may be transferred by a dry heparinized pipette to a small heparinized test-tube and thence to the narrow-gauge Meyerstein haematocrit tube which requires less blood than the Wintrobe tube with its wider bore

The estimated haematocrit is corrected for trapped plasma (*see* legend, Fig 48) and the corrected value is compared with that of the mean normal venous haematocrit for the patient's age, weight or preferably height from a chart of mean normal values (Fig 48) This chart also includes the mean normal values for the whole body haematocrit, plasma volume and red cell volume Assuming that the red cell volume has remained unchanged the patient's plasma volume can be calculated and the deficit in the volume, that is the degree of oligaemia, assessed The rate of loss of plasma from the circulation (in millilitres per hour) is estimated from the number of hours since burning if this was recent The rate of transfusion is adjusted according to the calculated deficit in the plasma volume, the

Fox, C. L. (1944) *J Amer med Ass.*, 124, 207
— and Baer H (1947). *Amer J Physiol.*, 151 155
— and Keston, A. S. (1945) *Surg Gynec Obstet.*, 80 561
Gefter L. M., and Milunkevitch, G F (1949) *Khirurgia*, No 4 26
Gibson, T., and Brown, A. (1945). In *Studies of Burns and Scalds* M R C. Special Report Series No 249
Gilmore, J P (1955) *U.S Naval Med. Field Res Lab.*, 6, 159
— and Handford S. W (1956) *J appl Physiol.*, 8, 393
Gjessing, E. C., and Chanutin, A. (1947). *J biol Chem.* 169 657
Gordenko A. N (1945). *Biull. eksp biol med.*, 19 30
Graber L G (1957) Personal communication.
Green, H N., Stoner H B Whiteley H J and Eglin, D (1949) *Clin Sci* 8, 56
Hardy, J D Lovelace J R., Jabbour E. and Bramlitt, E. E. (1955) *Amer Surg* 21 969
Harkins, H. N (1934) *Proc Soc exp Biol., N Y.*, 31 994
— (1935). *Ann. Surg.*, 102, 444
— (1954). *Surg Clin. N Amer.*, 34, 1313
Hechter O Bergman, H C., and Prinzmetal, M (1945) *Amer Heart J.*, 29 484
Keeley J L., Gibson, J G., and Pijoan, M (1939) *Surgery* 5, 872.
Keyser J W (1948). *Ann Surg.*, 127 605
Leach, E. H Peters, R. A. and Rossiter R. J (1943) *Quart J exp Physiol* 32, 67
Lee, W E. Wolff W A. Saltonstall H. and Rhoads, J E. (1942) *Ann Surg.*, 115 1125
Lischer C., Elman, R. and Davey H W (1944) *War Medicine* 5 43
Lombard, P and Montpellier J (1937). *Pr méd.*, 45, 1424
Lowdon, A. G R., McKail, R. A. Rae, S. L., Stewart, C. P and Wilson, W C. (1939). *J Physiol.*, 96, (Proc.) 27
McIver M. A. (1933) *Ann. Surg* 97 670
Markley, K. Bocanegra, M., Bazan, A., Temple, R. Chiappori, M., and Morales, G (1956) *J Amer med. Ass.*, 161 1465
Millican, C., Tabor H., Stohlman, E. F and Rosenthal, S M (1952) *Amer J Physiol.* 170, 187
Moore, F D Evans, R. E., and Ball, M. R. (1948) *Ann. Surg.*, 128, 266.
Moyer, C. A. (1953) *Ann. Surg.*, 137 628
— Coller F A. Iob V., Vaughan, H H., and Marty D (1944) *Ibid.*, 120, 367
Noble, R. P and Gregersen, M. I (1946) *J clin. Invest.*, 25, 172.
Prendergast, J J Fenichel R. L. and Daly B. M (1952) *Arch Surg.*, 64, 733
Presman, D L., Janota, M., Weston, R. E., Levinson, S O and Necheles, H (1943). *J Amer med. Ass.*, 122, 924
Prinzmetal, M. Bergman, H C., and Hechter O (1944). *Surgery* 16, 906
Rosenqvist, H (1947) *Acta. chir scand.*, Suppl., 124
Rosenthal, S M (1943). *U.S Publ Health Rep.*, 58, 513 1429
— and Tabor H (1945) *Arch. Surg.*, 51, 244
Schuevers, J (1936) *Arch int Pharmacodyn.*, 52, 452.
Sevitt, S (1949 and 1954). Unpublished observations.
Simonart, A. (1930). *Arch int Pharmacodyn.* 37 269
Tabor, H., and Rosenthal, S M (1945). *U.S Pub Health Rep* 60 373 401
— Kabat, H., and Rosenthal, S M (1944). *Ibid.*, 59 637
Tappeiner H. (1881). *Z med. Wiss.*, 19 385 401
Taylor F H L., Levenson, S. M., Davidson, C. S., Browder N C., and Lund, C C (1943). *Ann. Surg.*, 118, 215
Tenery R M (1941) *Surg Gynec Obstet* 72, 1018.
Topley E. and Jackson, MacG (1957) *J clin Path.*, 10, 1
Trusler H M., Egbert, H L., and Williams, H S (1939) *J Amer med. Ass.*, 113, 2207

current rate of loss of plasma and subsequent changes in the haematocrit value Finally the transfusion may be stopped after 24 hours if only small intravenous volumes are necessary to maintain a normal haematocrit value, fluids by mouth should be continued

However, it cannot be overstressed that calculations based only on the haematocrit value may seriously underestimate the degree of plasma oligaemia when there is a simultaneous fall in the red cell volume For this reason blood volume determinations are of considerable value in controlling the intravenous therapy of extensively burned patients in whom transfusion of whole blood as well as plasma is desirable (Chapter 15)

(2) *The rate of flow of urine* is estimated after passing an indwelling catheter, which should be left *in situ* for 48 hours In adults a flow of 50–100 millilitres per hour is satisfactory or generous but these figures may be difficult to obtain or maintain without overzealous transfusion An urinary output below 25 millilitres per hour is inadequate Oligaemia produces oliguria and the latter can usually be prevented by restoring and maintaining a normal blood volume (Chapter 13)

REFERENCES

Abbott, W E , Pilling, M A , Griffin, G E , Hirschfeld, J W , and Meyer, F L (1945) *Ann Surg* , **122,** 678

Anderson, A B , and Semeonoff, E (1945) In *Studies of Burns and Scalds,* M R C Special Report Series No 249, 166

Baraduc, H (1862) *Des causes de la mort a la suite des brûlures superficielles,* Paris

Beard, J W , and Blalock, A (1931) *Arch Surg* , **22,** 617

Black, D A K (1940) *Brit med J* , **2,** 693

Blalock, A (1931) *Arch Surg* , **22,** 610

Brooks, J W , Robinett, P , Largen, T L , and Evans, E I (1951) *Surg Gynec Obstet* , **93,** 543

Bull, J P , and England, N W J (1954) *Lancet,* **2,** 9

— and Jackson, D McG (1952) *Brit med J* , **1,** 1018 and 1078

— Ricketts, C , Squire, J R , Maycock, D d'A , Spooner, S J L , Mollison, P L , and Patterson, J C S (1949) *Lancet,* **1,** 134

Clark, E J , Peters, R A , and Rossiter, R J (1945) *Quart J exp Physiol* , **33,** 113

Cope, O , and Moore, F D (1944) *J clin Invest* , **23,** 241

— — (1947) *Ann Surg* , **126,** 1010

— Graham, J B , Moore, F D , and Ball, M R (1948) *Ibid* , **128,** 1041

Courtice, F C (1946) *J Physiol* , **104,** 321

Davidson, E C (1926) *Arch Surg* , **13,** 262

— and Matthew, C W (1927) *Ibid* , **15,** 265

Davies, J , and Topley, E (1956) *Clin Sci* , **15,** 135

Demidova, M N , Maslennikova, G M , and Kachanova, E V (1949) *Khirurgia,* No 4, 22

Elkington, J R , Wolff, W A , and Lee, W E (1940) *Ann Surg* , **112,** 150

Fine, J , and Seligman, A M (1944) *J clin Invest* , **23,** 720

Fogelman, M J , and Wilson, B J (1955) *Surg Forum, Amer Coll Surg* , **5,** 762

CHAPTER 11

BURN SHOCK MISCELLANEOUS FACTORS

A VARIETY of factors other than plasma oligaemia have been postulated as initiating or sustaining influences in the pathogenesis of burn shock Some of these are purely of historic interest and were suggested before the importance of oligaemia was recognized and those without factual evidence will not be discussed here The others which require some discussion are (1) the influence of nervous activity with special regard to primary shock haemoconcentration and cholinesterase, (2) visceral congestion (3) a general increase in capillary permeability (4) *capillary thrombosis and embolism* (5) *the sludging* of blood and (6) the influence of adenosine compounds The loss of red cell mass, which can play an important part in oligaemia is discussed in Chapter 15

NERVOUS ACTIVITY

Certain observations have shown that burning activates or modifies numbers of reflexes, some of which influence the body s resistance whilst others have no apparent significance McMaster and Hudeck (1932) found that when one ear of a mouse was burned the other ear also became hyperaemic, a process which must have been due to reflex activity Nervous activity can modify the haemodynamic changes after burning Mukhin (1947) found that the initial rise in arterial pressure and pulse rate following severe burns in dogs was less when the animals were burned under anaesthesia than when anaesthesia was not used and that during the subsequent hypotensive phase an injection of adrenaline produced a greater rise in blood pressure in the previously anaesthetized animals. Other workers had found that the temporary hypertension which follows burning was prevented by prior section of the spinal cord (Kabat and Hedin 1942) or by previous denervation of the burned area (Olson and Necheles 1943)

Nervous activity may also be involved in visceral congestion (*vide infra*) In other chapters the influence of central and autonomic nervous stimulation on the kidneys endocrine glands and other organs is discussed

Primary shock.—In man primary or nervous shock has been greatly overstressed and probably it has been often confused with a relatively

Underhill, F P, and Fisk, M E (1930) *Amer J Physiol*, **95**, 330
— — and Kapsinow, R (1930) *Ibid*, **95**, 302, 315, 325, 334, 339, 348 and 364
— Carrington, G L, Kapsinow, R, and Pack, G T (1923) *Arch intern Med*, **32**, 31
Weiner, D O, Rowlette, A P, and Elman, R (1936) *Proc Soc exp Biol, N Y*, **34**, 484
Wilson, W C, and Stewart, C P (1939) *Trans med-chir Soc Edinb*, **46**, 153

spinal cord at the twelfth thoracic segment a procedure which cut off the afferent supply to the hind limbs and may have prevented splenic contraction There was no difference between the mortalities of the transected and non transected animals On the other hand certain burns which produce an increase of permeability in intact skin fail to do so in denervated skin (Sevitt, 1954) which suggests that intact peripheral nerves increase the reactivity of the skin to heat and might increase the amount of plasma lost into the burn In this connexion the early pain after shallow burning may be important and the use of local or regional procaine anaesthesia advocated by Brumstein and Goriaeva (1941) and Sarkisov (1949) might have some significance

Cholinesterase and acetylcholine—A number of workers have investigated the cholinesterase activity of the blood after experimental burns on the supposition that changes in its concentration might influence the circulatory effects of burn shock (Frommel and Piquet, 1945 Stüttgen 1947 Schümmelfeder 1947) An increased activity might retard the fall in blood pressure by a more rapid destruction of acetylcholine in the cholinergic vasodilator nerve endings of blood vessels or by opposing parasympathetic activity on the heart, whilst a decreased activity might hasten hypotension The experimental results are conflicting. Frommel and Piquet (1945) found that thermocauterization of guinea pigs reduced the serum cholinesterase but that extensive scalding had little or no effect Stüttgen (1947) however reported a lowered activity whilst Schümmelfeder (1947) working with severely burned dogs found a moderate increase in activity associated with a profound fall in blood pressure

Acetylcholine was also demonstrated in the blood of burned dogs but the experiments indicated that its appearance resulted from the circulatory disturbance and was not its cause (Hoppe-Seyler and Schümmelfeder 1946)

Visceral congestion.—Many observers including the author have found a considerable congestion of the lungs, brain alimentary tract, liver spleen kidneys, adrenals and other organs in burned animals (Simonart, 1930 Prinzmetal and Bergman 1945) and in fatally burned subjects (Pack, 1926 Erb Morgan and Farmer 1943) The organs may be red and swollen the congestion involving an opened up capillary bed and microscopically the capillaries are full of red cells Many of these changes seem to commence soon after burning and are more advanced the more prolonged the survival during the first few days It may be argued that the trapping of sufficient blood in the viscera would reduce the venous return produce a functional oligaemia lower the cardiac output and increase the degree of shock

rapid onset of oligaemic shock which may occur under special conditions (Chapter 9) Nervous shock nevertheless does occur occasionally but it is less uncommon in experimental animals than in man Sometimes when animals are burned extensively they die within a few minutes, presumably from neural shock The cardiovascular disturbances within a few minutes of burning were studied in anaesthetized dogs by Dobson and Warner (1955) who found a rapid and considerable reduction of the cardiac output, which sometimes fell to one-seventh of its pre-scald value, this was not accompanied by bradycardia or significant hypotension but there was an immediate decrease of the circulation through the liver and probably the kidneys and brain The cardiac effect was probably central in origin and reflexly initiated since it was too rapid for oligaemia to have been responsible Parallel changes in man are not known but immediate cardiovascular collapse in dogs is a different phenomenon from the less rapid development of oligaemic shock in man

In man, fright and pain from burning may produce a fainting turn but the patient usually recovers quickly and the condition is rarely seen by the hospital doctor Syncope is accompanied by hypotension, pallor and usually bradycardia and the phenomenon is said to be a "vaso-vagal attack" resulting from nervous stimulation or inhibition Rapid death after burning may occasionally result from this, but when death occurs in a large fire, particularly in a confined space, other causes such as carbon-monoxide poisoning or acute hyperpotassaemia from body hyperthermia may be responsible (Chapters 9 and 19)

Haemoconcentration—Some workers have claimed that nervous activity modifies the degree of haemoconcentration and by inference the degree of oligaemia Simonart (1930) thought that the depth of anaesthesia during the burning influenced the subsequent haemoglobin value When the animals were deeply anaesthetized the degree of haemoconcentration after burning was found to be less than that found when light anaesthesia was used Moreover, early haemoconcentration could be prevented by previous decerebration or destruction of the spinal cord These observations could be related to the findings of Mukhin (1947) that there was an initial rise in the blood volume of dogs burned without anaesthesia, and all the observations could be explained by acute splenic contraction which would produce a rapid increase in the circulating red cell volume Kabat and Hedin (1942) found that the degree of haemoconcentration after a deep burn of the hind limb of cats was lessened by prior transection of the

GENERAL INCREASE OF CAPILLARY PERMEABILITY

It has been asserted that haemoconcentration after burning is partly the result of a generalized leakage of fluid from the circulation associated with the generalized congestion of the visceral capillaries (Simonart, 1930). This recalls the thesis of Moon (1938) on traumatic shock, but the main evidence is against this hypothesis even though an increased capillary permeability of the internal viscera was claimed by Netsky and Leiter (1943). They found that horse serum injected intravenously into dogs appeared more rapidly in the cervical and thoracic duct lymph when the animal was burned than in normal animals. Other workers have denied that any permeability change occurs in the visceral or general body capillaries. Fine and Seligman (1944) studied dogs in shock after burning, haemorrhage or application of a limb tourniquet by injecting plasma protein tagged with radioactive iodine. Plasma protein did not escape into the internal viscera even during the irreversible phase of shock although protein appeared in considerable quantities in the burned or injured area. Moreover the flow of lymph from unburned areas does not increase after burning (Glenn, Muus and Drinker, 1943) nor does the radioactivity of the lymph from unburned areas rise abnormally after the injection of radioactive azo-dyes coupled to plasma protein (Cope and Moore, 1944). Furthermore ophthalmoscopic examination of burned dogs failed to reveal peripapillary oedema (Humblet and Barac, 1946).

The contradictory results might be explained by the different extents of burning inflicted by different workers. The animals of both Simonart and of Netsky and Leiter were extensively burned, but the burns inflicted by the other workers (except Humblet and Barac) were usually confined to one limb. Nevertheless it may be concluded that if a generalized increase of capillary permeability does occur after burning *it is not of great significance in the production of* oligaemic shock.

CAPILLARY THROMBOSIS AND EMBOLISM

Some of the earlier investigators believed that a widespread capillary thrombosis or thrombo-embolism occurred after burning and was responsible for many of the pathological changes found (Baraduc, 1863; Fränkel, 1889; Silbermann, 1889). Thrombi in the capillaries of the alimentary tract, kidneys, liver, lungs and brain might, it was said, prove fatal and Pack (1926) suggested that plugging of the minute vessels in the lungs might obstruct the pulmonary circulation and throw an additional load on the heart. The predisposition of burned patients to thrombosis was said to result

Abell and Page (1943) observed microscopically the changes in the mesenteric vessels of burned dogs and cats, their findings are of particular relevance The larger and smaller arteries and the larger veins became constricted within an hour or two of burning, the arterio-venous anastomoses narrowed and the blood was deviated into the capillary bed Soon there was little or no movement of blood in the smaller arteries and veins Abell and Page point out that if the changes in the mesenteric vessels are typical of those in other parts of the body, they would result in a progressively diminishing blood flow to the peripheral tissues due to a reduced venous return to the heart Furthermore, serial studies of the red cell mass in burned patients have sometimes shown a rise in the total red cell volume a few days after burning, which suggests that trapped cells have been mobilized and returned to the circulation (Topley, 1956) The return of blood is probably more frequent and larger than actually observed because it would be obscured in total red cell estimations when there is a simultaneous disappearance of other red cells (Chapter 15)

Oligaemia from acute visceral congestion may explain in part the observations of Prinzmetal, Bergman and Hechter (1944) and Prinzmetal and Bergman (1945) They described a form of burn shock in rats apparently distinct from that resulting from plasma loss due to burn oedema When a single hind limb was immersed in water at 75°C for 10 seconds it became very oedematous but clinical shock did not occur and the animals survived, however, when the limb was scalded at 100°C for 2 or 3 minutes many animals died 12–24 hours later, even though the limb was not greatly swollen The shock was associated with a quick onset of visceral congestion, a reduction in the bleeding volume indicative of oligaemia but with little or no haemoconcentration Acute visceral congestion may have reduced the bleeding volume but other factors may also have played a part in causing death of these animals These are (1) oligaemia due to a considerable red cell destruction, since the degree of red cell destruction is likely to be greater when burning is more prolonged and at a higher temperature (Raker and Rovit, 1954) and (2) acute hyperpotassaemia from the considerable red cell lysis which must have occurred

Pathogenesis —Local spinal reflexes may be involved because Brown-Sequard (1858) found that congestion of the viscera after burning was prevented by previous division of the nerves to the burned hind limb or by section of the lumbar cord but not by section of the cord above the level of the burning

ADENOSINE COMPOUNDS

After the discovery that the shock producing factor in extracts of muscle is adenosine triphosphate (A T P) (Green 1943) Green and Stoner and their co-workers studied the possible release of this nucleotide into the blood stream after various forms of experimental injury Biochemical investigations of the various components of A T P (adenosine-equivalent, phosphate and pentose) showed that all of them rapidly increased in the blood (for references *see* Green and his colleagues 1949) and this suggested that release of A T.P from muscle may contribute to the shock syndrome Similar changes were found in the blood after scalding experimental animals (Green Stoner and Bielchowsky 1949 Stoner and Green 1949) and Cullumbine (1947) also found a rapid increase in the adenosine equivalent of the blood in burned rabbits Investigation of battle casualties during World War II including a group of burned soldiers, also showed significant increases in the blood of the components of A.T P (Green and his colleagues, 1949)

Release of A T P from muscle probably cannot account for the biochemical changes after superficial burning, but since erythrocytes are rich in adenyl compounds it is likely that injury or lysis of red cells circulating through the burned skin is responsible for the observed biochemical changes in the blood

It is undecided whether the released adenosine compounds contribute to burn (or traumatic) shock. This will depend on whether they exist in the blood in the potent conjugated form of A.T P or as a mixture of relatively innocuous substances or basic fragments Biochemical studies have shown that the extracellular nucleotide is rapidly decomposed by dephosphorylation and deamination so that if A.T P is released into the blood it is probably rapidly broken down

REFERENCES

Abell, R. G and Page, I. H (1943) *Surg Gynec Obstet.*, 77 348
Baraduc, H (1863) *Union med. Paris* May 19
Brooks, F Dragstedt, L. R. Warner L. and Knisely M (1950) *Arch Surg.*, 61, 387
Brown-Séquard, E. (1858) *Lancet* 2, 545
Brunstein, M S., and Gorlaeva, A. V (1941) *Arch. Sci Biol.*, 62, 62.
Cope, O., and Moore, F D (1944) *J clin. Invest* 23, 241
Cullumbine, H (1947) *J Path Bact.*, 59 477
Dobson, E L., and Warner G F (1955) *Fed. Proc.*, 14, 39
Erb I H Morgan, E. M., and Farmer A. W (1943) *Ann. Surg.*, 117 234
Fine J and Seligman, A. M (1944) *J clin Invest.*, 23, 720
Fränkel E. (1889) *Dtsch. med. Wschr*, 15, 22.
Frommel, E. and Piquet, J (1945). *Schweiz. med Wschr.*, 75, 593
Glenn, W W L., Muus, J., and Drinker C. K. (1943). *J clin. Invest.*, 22, 451
Green, H. N (1943) *Lancet* 2, 147

from venous stasis viscidity of the blood and leucocyte disintegration, and Hayem (1889) thought that there were three kinds of thrombi—platelet clots, fibrin clots and "thromboses par précipitation" These ideas which are now largely of historic interest, arose before the importance of oligaemia was properly recognized and because the cause of death after burning was uncertain Many of the visceral changes which were attributed to emboli are now known to be due to other causes More recently Kabat and Levine (1942) again raised the idea that capillary embolism was a lethal factor in burns and thought that it might account for sudden unexplained death However as they did not demonstrate capillary emboli in their animals their hypothesis remains without substance

This does not mean that capillary thrombo-embolism does not occur On the contrary distinct glomerular capillary thrombi were found by Sevitt (1956) in about 10 per cent of patients most of whom died on the second day after burning (Chapter 14) but it is doubtful if they are of much significance

Fat embolism.—Pulmonary fat embolism was found in about 40 per cent of fatally burned patients by the author but it was very slight and only incidental The source of the fat is probably from heat-ruptured fat cells in the subcutaneous tissues of the burned area

THE SLUDGING OF BLOOD

Brooks and his colleagues (1950) observed an interesting physical alteration in the circulating blood of burned animals and in one patient by direct microscopy of the bulbar and other vessels Instead of the normal laminar, streamlined flow the erythrocytes were clumped into rigid smooth masses 25–50 μ in diameter which tumbled and turned as they progressed This *sludging* of blood as they termed it was previously found in many other conditions, after burning it increased in degree with passage of time It was associated with a decreased rate of blood flow, with sacculation and tortuosity of small vessels lining of the endothelial surface by leucocytes and the formation of pseudo-thrombi The latter were really clumped masses of red cells which lodged temporarily or permanently in a small vessel They suggested that sludging caused considerable slowing of the blood stream stasis of vessels, pseudo-thrombi, exudation of fluid and other phenomena that sludging resulted in anoxic changes in the endothelium and tissues and played an important part in the production of shock Most of these claims seem premature but the exact significance of sludging is unknown and further investigations are desirable

ADENOSINE COMPOUNDS

After the discovery that the shock producing factor in extracts of muscle is adenosine triphosphate (A T P) (Green 1943) Green and Stoner and their co-workers studied the possible release of this nucleotide into the blood stream after various forms of experimental injury Biochemical investigations of the various components of A T P (adenosine-equivalent phosphate and pentose) showed that all of them rapidly increased in the blood (for references *see* Green and his colleagues 1949) and this suggested that release of A T P from muscle may contribute to the shock syndrome Similar changes were found in the blood after scalding experimental animals (Green Stoner and Bielchowsky 1949 Stoner and Green 1949) and Cullumbine (1947) also found a rapid increase in the adenosine equivalent of the blood in burned rabbits Investigation of battle casualties during World War II including a group of burned soldiers also showed significant increases in the blood of the components of A.T P (Green and his colleagues 1949)

Release of A.T.P from muscle probably cannot account for the biochemical changes after superficial burning but since erythrocytes are rich in adenyl compounds it is likely that injury or lysis of red cells circulating through the burned skin is responsible for the observed biochemical changes in the blood

It is undecided whether the released adenosine compounds contribute to burn (or traumatic) shock This will depend on whether they exist in the blood in the potent conjugated form of A T P or as a mixture of relatively innocuous substances or basic fragments Biochemical studies have shown that the extracellular nucleotide is rapidly decomposed by dephosphorylation and deamination so that if A.T P is released into the blood it is probably rapidly broken down

REFERENCES

Abell, R G and Page I H. (1943) *Surg Gynec Obstet.*, 77 348
Baraduc, H (1863) *Union med. Paris* May 19
Brooks, F., Dragstedt, L. R. Warner L. and Knisely M. (1950) *Arch Surg.*, 61, 387
Brown-Séquard E. (1858) *Lancet* 2, 545
Brunstein, M S and Gorraeva, A. V (1941) *Arch. Sci Biol* 62, 62.
Cope, O., and Moore, F D (1944) *J clin Invest* 23, 241
Cullumbine, H (1947). *J Path Bact* 59 477
Dobson, E. L. and Warner G F (1955) *Fed. Proc.*, 14 39
Erb I H Morgan, E. M., and Farmer A. W (1943) *Ann Surg* 117 234
Fine, J and Seligman, A. M (1944) *J clin. Invest* 23, 720
Fränkel, E. (1889). *Dtsch. med Wschr.*, 15, 22
Frommel, E., and Piquet, J (1945) *Schweiz. med. Wschr* 75, 593
Glenn, W W L., Muus, J and Drinker C. K. (1943) *J clin Invest* 22, 451
Green, H N (1943) *Lancet* 2, 147

Green, H N, Stoner, H B, and Bielchowsky, M (1949) *J Path Bact*, **61**, 101
— — Whiteley, H J, and Eglin, D (1949) *Clin Sci*, **8**, 65
Hayem, G (1889) *Du sang et des alterations anatomiques* Paris
Hoppe-Seyler, A, and Schummelfeder, N (1946) *Z Naturforsch*, **1**, 696
Humblet, M, and Barac, G (1946) *C R Soc Biol*, **140**, 1210
Kabat, H, and Hedin, R F (1942) *Proc Soc exp Biol Med*, **49**, 114
— and Levine, M (1942) *Science*, **96**, 476
McMaster, S, and Hudeck, P D (1932) *J exp Med*, **55**, 239, 431
Moon, V H (1938) *Shock and related capillary phenomena* New York
Mukhin, I A (1947) *Khirurgia*, No 5, 30
Netsky, M G, and Leiter, S S (1943) *Amer J Physiol*, **140**, 1
Olson, W H, and Necheles, H (1943) *Amer J Physiol*, **139**, 574
Pack, G T (1926) *Arch Path Lab Med*, **1**, 767
Prinzmetal, M, and Bergman, H C (1945) *Clin Sci*, **5**, 205
— — and Hechter, O (1944) *Surgery*, **16**, 906
Raker, J W, and Rovit, R L (1954) *Surg Gynec Obstet*, **98**, 169
Sarkisov, M A (1949) *Sovet Med*, **13**, 19
Schummelfeder, N (1947) *Arch exp Path Pharm*, **204**, 567, 626
Sevitt, S (1954) *Proc R Soc Med*, **47**, 225
— (1956) *J Clin Path*, **9**, 222
Silbermann, O (1889) *Cent med Wiss*, **27**, 513
Simonart, A (1930) *Arch intern Pharmacodyn*, **37**, 269
Stoner, H B, and Green, H N (1949) *J Path Bact*, **61**, 114
Stuttgen, G (1947) *Klin Wschr*, **24–25**, 758
Topley, E (1956) Personal communication

CHAPTER 12

TOXAEMIA

An hypothesis which becomes dispossessed by new facts dies an honour able death and if it has already called up for examination those truths by which it was annihilated it deserves a moment of gratitude

JOHN HUNTER

THE concept of acute toxaemia is that a toxin formed in the skin after burning is absorbed into the circulation where it produces general effects and may lead to death The idea apparently originated from Avdakoff (1876) who reported that the blood of a burned animal was toxic to other animals The number and variety of toxins which have been reported in the blood urine or burned skin is legion and includes proteoses peptones toxalbumin ptomaines formic acid methyl guanidine, ammonia, tyramine histamine and many others the large number indicating the elusive nature of the toxin

The concept was developed to explain certain clinical and pathological changes Vomiting fever hyperpyrexia an altered mental state a rapid weak pulse respiratory distress and perhaps jaundice may develop 12–24 hours after burning and were considered by Wilson Macgregor and Stewart (1938) to be toxaemic in origin Degenerative changes developing in lymphoid tissue the adrenals liver and other organs as well as the early leucocytosis were compared with the toxaemic effects of bacterial infections and were considered to be the result of a burn toxin (Bardeen 1898 Weiskotten 1919 Olbrycht, 1924 Wilson Macgregor and Stewart, 1938)

A logical development of the theory was the introduction of tannic acid therapy by Davidson (1925) to coagulate the entire burned surface so that potentially toxic substances might be precipitated locally and their absorption prevented

BASIS OF THE TOXAEMIA THEORY

The literature dealing with toxaemia is voluminous but the concept is based on four main kinds of experimental evidence

(1) Injection of the blood or serum of burned animals into normal animals produces severe illness or death (Parascandolo 1904 Pfeiffer 1905 Bernhard, 1936) Pfeiffer whose work is often quoted claimed that neurotoxic and necrotoxic protein products were

present This work has not gone unchallenged and other investigators have found that injection or transfusion of blood from burned animals into others has no toxic effect (Stockis, 1903, Harrison and Blalock, 1932) Furthermore Wood (1940) showed that lymph collected from a burned part had no vaso-depressive properties It should be mentioned that the importance of preventing bacterial contamination has probably invalidated many observations which appear to support toxaemia

(2) Injection of extracts of burned skin or the injection of burn exudate or vesicle fluid into normal animals produces toxic or lethal effects (Robertson and Boyd, 1923, Bernhard, 1936, Wilson and his colleagues, 1936–7) The work of Robertson and Boyd was repeated by Underhill and Kapsinow (1931) and was shown to be technically at fault Moreover, Harrison and Blalock (1932) found that transplantation of burned skin to normal animals had no effect on the latter The observation by Wilson and his colleagues that the oedema fluid from the burned skin of rabbits developed lethal properties for other rabbits and mice at about 48 hours after burning was confirmed by Cullumbine, McDonald and Simpson (1947), but the lethal intravenous dose for rabbits was as much as 10 millilitres Further evidence against a skin toxin was provided by Harkins, Wilson and Stewart (1935) who isolated a depressor substance from skin but showed that it was present in extracts of burned and normal skin in about the same concentration

(3) Cross-circulation experiments by which the blood streams of two animals are connected and one of them is subsequently burned have shown that the unburned partner also develops a severe illness or dies (Vogt, 1912a and b, Cevario, 1921, Vaccarezza, 1922, Christophe, 1939) These results could be adequately explained on the basis of oligaemia since the development of a low blood volume through plasma loss in the burned animal would produce a low circulatory volume in the other animal Vogt's finding that separation of the animals a few hours after burning prevents the death of the unburned partner is also consistent with the prevention of a fatal oligaemia

(4) Exclusion of the burned part from the general circulation either by ligature of the main vessels to the part, or by early excision of the area or amputation of the burned limb prevents a fatal outcome in the animal (Rydigier, 1888, Salvioli, 1891, Stockis, 1903, Vaccarezza, 1922) These experiments which were interpreted as preventing a locally liberated toxin from reaching the circulation, can be just as well explained by the prevention of exudation into the burned part and the prevention of oligaemia

ABNORMAL SUBSTANCES

The compounds released or formed after burning include the following substances

Haemoglobin is released into the plasma from heat affected red cells circulating through the skin at the time of burning. Haemoglobinaemia and haemoglobinuria are of importance in the pathogenesis of renal failure (Chapter 14)

A pyronin-stainable substance (probably related to ribonucleic acid) and *nuclear nucleoprotein* was demonstrated histologically by Leach Peters and Rossiter (1943) in burned skin during the course of disintegrative necrosis of epidermal cells (Chapter 2)

Skin proteinase is released by heat injured epidermis (Beloff and Peters 1945)

Polypeptides with leukotaxic properties have been demonstrated in burn exudate and skin (Cullumbine and Rydon 1946)

Histamine liberation has been confirmed (Rosenthal and Minard, 1939 Kellaway 1947 Rosenthal and his colleagues 1957)

The possible roles played by skin proteinase, leukotaxine and histamine in the pathogenesis of the inflammatory changes in burned skin are discussed in Chapter 3

Abnormal proteins including *gelatin* have been described Perlmann Glenn and Kaufman (1943) detected an unusual protein in the lymph draining from the burned area of dogs and found that it migrated with half the speed of *gamma* globulin Its origin and identity remained unknown until the proteins diffusing *in vitro* after heating dermatome slices of skin were studied by Rosenthal and his colleagues (1957) A protein resembling gelatin in its hydroxyproline content and electrophoretic behaviour diffused out from the skin when it was subsequently placed in fluid at 37°C, particularly when the immersion had been at relatively high temperatures for prolonged periods Significantly its electrophoretic mobility resembled that of the protein described by Perlmann and his colleagues and it is reasonable to conclude that heat-denatured collagen was the source Smaller amounts of other proteins were also liberated *in vitro* including proteins containing hexose and sialic acid"

The *peptidase* activity of lymph from a burned area in dogs and of human blister fluid was found to be increased (Zamecnic, Stephenson and Cope, 1945) This may be related to the finding of free amino acids in exudates which also contain leukotaxine polypeptides (Spector 1951)

A *vasoconstrictive* property is developed by the plasma of burned dogs (Page 1943)

The *glycoprotein* value of the serum after burning is raised (Keyser 1952)

The *peptide* excretion in the urine is increased (Baar 1956)

present This work has not gone unchallenged and other investigators have found that injection or transfusion of blood from burned animals into others has no toxic effect (Stockis, 1903, Harrison and Blalock, 1932) Furthermore Wood (1940) showed that lymph collected from a burned part had no vaso-depressive properties It should be mentioned that the importance of preventing bacterial contamination has probably invalidated many observations which appear to support toxaemia

(2) Injection of extracts of burned skin or the injection of burn exudate or vesicle fluid into normal animals produces toxic or lethal effects (Robertson and Boyd, 1923, Bernhard, 1936, Wilson and his colleagues, 1936–7) The work of Robertson and Boyd was repeated by Underhill and Kapsinow (1931) and was shown to be technically at fault Moreover, Harrison and Blalock (1932) found that transplantation of burned skin to normal animals had no effect on the latter The observation by Wilson and his colleagues that the oedema fluid from the burned skin of rabbits developed lethal properties for other rabbits and mice at about 48 hours after burning was confirmed by Cullumbine, McDonald and Simpson (1947), but the lethal intravenous dose for rabbits was as much as 10 millilitres Further evidence against a skin toxin was provided by Harkins, Wilson and Stewart (1935) who isolated a depressor substance from skin but showed that it was present in extracts of burned and normal skin in about the same concentration

(3) Cross-circulation experiments by which the blood streams of two animals are connected and one of them is subsequently burned have shown that the unburned partner also develops a severe illness or dies (Vogt, 1912a and b, Cevario, 1921, Vaccarezza, 1922, Christophe, 1939) These results could be adequately explained on the basis of oligaemia since the development of a low blood volume through plasma loss in the burned animal would produce a low circulatory volume in the other animal Vogt's finding that separation of the animals a few hours after burning prevents the death of the unburned partner is also consistent with the prevention of a fatal oligaemia

(4) Exclusion of the burned part from the general circulation either by ligature of the main vessels to the part, or by early excision of the area or amputation of the burned limb prevents a fatal outcome in the animal (Rydigier, 1888, Salvioli, 1891, Stockis, 1903, Vaccarezza, 1922) These experiments which were interpreted as preventing a locally liberated toxin from reaching the circulation, can be just as well explained by the prevention of exudation into the burned part and the prevention of oligaemia

ABNORMAL SUBSTANCES

The compounds released or formed after burning include the following substances

heated to 120°C produced antisera which precipitated similarly heated proteins of this and other mammalian species

This, however is not auto-immunization but the recent work of Fedorov (1956) suggests not only that auto-immunization is a regular accompaniment of burning but also that the flooding of the body with antigens derived from the burned area may be responsible for part of the burn illness He reported the discovery of specific protein antigens in the blood and tissues of burned animals which apparently had been absorbed from the heat injured skin Serum and blood from dogs which had recovered from burns were transfused into other burned dogs and special beneficial effects were claimed The circulation became normal the blood volume increased renal function improved, survival time was lengthened and acute mortality rate decreased Moreover the sera of healthy dogs previously injected with blood from burned animals was also said to have a pronounced therapeutic effect greater than that of the serum from non immunized animals Fedorov believed that the sera injected were immune sera containing antibodies against antigens liberated from the burned skin and that the protective effect in burned animals was partly or largely due to the neutralization of the flood of protein antigens released from the injured tissues

This new and interesting contribution to the concept of toxaemia, which has therapeutic implications requires confirmation before the present-day outlook reported above needs to be amended

REFERENCES

Avdakoff, (1876). *St Petersburg med. Wschr* Quoted by Stockis (1903)
Baar S (1956) *J clin. Path.* 9 144
Bardeen, C R. (1898) *Johns Hopk Hosp Rep.*, 7 137
Beloff A., and Peters R. A (1945) *J Physiol* 103 461
Bernhard E. (1936) *Z exp Med.*, 98, 278
Cevario L. (1921) *Pathologica*, 13, 12, 281
Christophe, L. (1939) *La mort des brulés* Paris.
Cullumbine, H., McDonald, F., and Simpson, M H (1947) *J Path Bact* 59 467
— and Rydon, H. N (1946). *Brit J exp Path.* 28, 33
Davidson, E. C. (1925) *Surg Gynec Obstet.*, 41 202.
Fedorov N A (1956) In *Proc 6th Congr Internat Soc Blood Transf* 44
Harkins, H N Wilson W C. and Stewart, C. P (1935) *Proc Soc exp Biol Med* 32, 913
Harrison W G and Blalock, A (1932) *Ann Surg* 96, 36.
Kellaway C H (1947). *Edin med. J* 54, 333
Keyser J W (1952). *J clin Path* 5 194
Landsteiner K. (1936) *The specificity of serological reactions* Springfield Thomas.
Leach, E. H., Peters, R. A., and Rossiter R. J (1943) *Quart J exp Physiol* 32, 67
Olbrycht J (1924) *Rév de med.*, 41 81
Page I H (1943) *Amer J Physiol.*, 139 386.
Paruscandolo K. (1904) *Wien med Wschr.*, 54 575

PRESENT-DAY OUTLOOK

The concept of toxaemia has lost ground mainly because of recent developments in knowledge which render the theory unnecessary It is now known that the jaundice and hepatic necrosis attributed to toxaemia were usually caused by the absorption of tannic acid applied to the burn (Chapter 22) Moreover, the physiopathological changes following burns are now better understood and a hypothetical toxin is required less and less to explain their pathogenesis The leading role of burn exudation in causing oligaemia and the circulatory disorder of shock has become clarified, the changes in the kidneys due to ischaemia and haemoglobinuria are better understood, the biochemical and metabolic disturbances involving electrolytes, nitrogen and carbohydrates do not require a toxin for their understanding, lymphoid degeneration is probably due to adrenocortical hormone activity, and the adrenal gland itself is now known to be hyperactive and not exhausted It may be that some of the toxaemic phenomena noted by Wilson, Macgregor and Stewart (1938) were the clinical counterpart of the acute katabolic response to injury Early fever and hyperpyrexia may also be due to the reduced ability of the skin (partly from burning and partly from vasoconstriction) to lose body heat, or may be neurogenic in origin The onset of other symptoms such as vomiting and dyspnoea may also be partly or wholly neurogenic, and acute mental effects probably result from anoxia due to oligaemia and cerebral swelling Furthermore bacteriological studies have shown that burns frequently and rapidly become contaminated with haemolytic streptococci, *Pseudomonas pyocyanea*, *Staphylococcus aureus* and other pathogenic bacteria, and bacterial infection or septicaemic invasion has been found responsible for the clinical toxaemia in many patients (*see* Chapter 6) Nevertheless certain symptoms are difficult to explain on the basis of our present knowledge and bacteria can only account for a proportion of the "toxaemic" cases but this does not mean that a toxin is at fault Extension of knowledge will clarify the pathophysiological basis of what is now poorly understood

The important problem of auto-immunization needs mention This might explain the frequent occurrence of a delayed eosinophilia in burned patients (Chapter 16) which may result from a sensitization of the body following the absorption of altered proteins from the burned area The production of an antiserum by the injection of proteins of the same species is difficult, but following various chemical alterations of the protein an immunological response is more readily obtained (Landsteiner, 1936) Of special interest is the observation of Uwazumi (1934) that immunization of rabbits with rabbit serum

CHAPTER 13

THE EXCRETION OF WATER AND ELECTROLYTES

JUST as the composition of normal urine reflects body physiology the composition of the urine of burned patients reflects their disordered function The changes associated with renal failure haemolytic anaemia, liver dysfunction and alterations in the metabolism of nitrogen and carbohydrate are discussed in their appropriate chapters

This chapter is concerned with the alterations in the flow and electrolyte composition of the urine which take place during the shock phase and the subsequent few days The pattern of changes is characteristic Soon after burning the output of urine declines together with the excretion of sodium and chloride but the excretion of potassium is unaffected or somewhat raised the reduction in output of water and salt lasts a few days and is followed by a diuresis Water and salt therapy can influence the details of this pattern but not its essence

WATER AND SALT RETENTION

Water retention.—The early reduction in the flow of urine has been known for many years Oliguria is discussed by Pack (1926) who related it to an impairment of kidney function and to plasma oligaemia, which is near to the present concept Oliguria is often severe in untreated animals and in patients receiving inadequate transfusion and may approach anuria. It is difficult to decide whether this is renal or extrarenal in origin particularly if death occurs within 2 or 3 days and either before uraemia has time to develop or an adequate flow of urine has returned indeed the borderline between extrarenal oliguria and that which may be associated with renal failure (Chapter 14) is often indistinct and may at times be artificial

An acute reduction in the flow of urine also occurs in patients who are adequately transfused by modern standards and who do not develop renal failure In patients treated in the Burns Unit in Glasgow (Anderson and Semeonoff 1945) and in Birmingham (Bull and England, 1954) the output of urine was usually 0 5–1 0 litre per day for the first 2–4 days and this is also the experience of

Perlmann, G E, Glenn, W W L, and Kaufman, D (1943) *J clin Invest*, **22**, 627
Pfeiffer, H (1905) *Virchows Arch*, **180**, 366
Robertson, B, and Boyd, G L (1923) *J Lab clin Med*, **9**, 1
Rosenthal, S R, and Minard, D (1939) *J exp Med*, **70**, 415
— Samet, C, Winzler, R J, and Shkolnik, S (1957) *J clin Invest*, **36**, 38
Rydigier, P (1888) *Dtsch med Wschr*, **2**, 1076
Salvioli, J (1891) *Virchows Arch*, **125**, 364
Spector, W G (1951) *J Path Bact*, **63**, 93
Stockis, E (1903) *Arch int Pharm*, **2**, 201
Underhill, F D, and Kapsinow, R (1931) *J Lab clin Med*, **16**, 823
Uwazumi (1934) *Arb Med Fak Okayama*, **4**, 53 Quoted by Landsteiner (1936)
Vaccarezza, R A (1922) *Comp rend Soc biol*, **86**, 1114
Vogt, W (1912a) *Virchows Arch*, **273**, 140
— (1912b) *Z exp Path*, **2**, 191
Weiskotten, H G (1919) *J Amer med Ass*, **72**, 259
Wilson, W C, Jeffrey, J S, Roxburgh, A N, and Stewart, C P (1936–7) *Brit J Surg*, **24**, 601
— Macgregor, A R, and Stewart, C P (1938) *Ibid*, **25**, 826
Wood, G P (1940) *Arch Surg*, **41**, 1038
Zamecnic, P C, Stephenson, M L, and Cope, O (1945) *J Biol Chem*, **158**, 135

rate of glomerular filtration may be associated for a time with a *raised* urinary output which indicates that the percentage of the filtered fluid reabsorbed by the renal tubules is less than normal At other times or in other patients a reduction in the urine flow is associated with a greater reduction in glomerular filtration Neverthe less the urinary output can often be maintained within reasonably normal limits by the early correction of oligaemia and the subsequent holding of the blood volume at the normal level—unless the irreversible oliguria of renal failure has occurred The interrelationship between blood volume, glomerular filtration rate of flow of urine and the associated haemodynamic factors such as cardiac output, blood pressure and vasoconstriction are undoubtedly complex particularly in burned subjects in whom frequent and rapid altera tions may be taking place

Sodium and chloride retention.—The excretion of sodium and chloride also declines after burning Within 12–24 hours the concentration of these solutes is low sometimes sodium and chloride almost disappear from the urine and their daily output usually falls to less than 20 milli-equivalents per day The fall in output usually lasts 3–6 days Reduction of chloride in the urine was first recorded by Davidson (1926) who inferred that sodium was also involved Subsequent studies on treated patients had confirmed Davidson s basic observation (Keyser 1948) and have shown that the sodium output is also greatly reduced (Fox, 1944 Moore and Ball 1952 Bull and England, 1954 Graber and Sevitt, 1957)

The pattern of sodium and chloride excretion may be influenced by therapy The giving of considerable amounts of sodium chloride during the first 24 hours to patients treated with plasma may delay the onset of a low chloride and sodium excretion by perhaps 12–24 hours and perhaps increase the subsequent low urinary concentra tions and output, but only a fraction of the extra salt is excreted and the total excretion remains low The effects of low and high intakes of sodium were compared by Bull and England (1954) A mean increase of intake of 259 milli-equivalents of sodium given to those with burns involving less than 30 per cent of the body area was associated with a mean increase of excretion of 52 milli-equivalents and in those with larger burns a mean increase of 551 milli-equivalents in the intake was associated with a mean increased excretion of 88 milli-equivalents Markley and his colleagues (1956) found that the retention of sodium and chloride was more prominent in patients given large doses of saline than in colloid treated patients given a low sodium chloride intake Thus the cumulative positive balance is

Monsaingeon (1949) and others Failure to excrete most of the transfused fluid produces a high positive balance of water which is mainly, if not entirely, stored in the burn oedema The main factors influencing the early flow of urine are (1) the volume and nature of the fluid administered and (2) the extent of burning If in extensively burned patients the rate of colloid transfusion is insufficient to maintain a relatively normal blood volume the rate of excretion of urine will fall, and in adults may be only 10 millilitres per hour, or less if transfusion is poor Moderate variations in the amount of colloid transfused or salt administered do not however greatly influence the daily output (Bull and England, 1954) but the hourly output is often significantly affected by increasing the rate of the drip Cope and Moore (1947) showed that when large transfusions of plasma and saline were given the urinary output often increased greatly, even up to several litres per day during the first 2 or 3 days, although most of the transfused fluid was not excreted The positive water balance was greatly increased and the burn oedema expanded considerably Markley and his colleagues (1956) compared the urine excretion of patients treated with intravenous colloid with the excretion of those given massive doses of saline In children, in whom the total fluid intake was equal in both groups, the output during the first and second day was greater in those receiving colloid In adults, in whom the volume of fluid intake was greater in the saline group, the urinary output was also greater in the saline group Fourteen per cent of the adults receiving colloid and 10 per cent of those receiving saline excreted less than 100 millilitres of urine per 24 hours and most of them had burns involving more than 50 per cent of the body area In less extensively burned adults the mean daily excretions were between 500 and 1,000 millilitres, the higher values in the saline group and the lower values in those receiving colloid In patients receiving colloid transfusion Bull and England (1954) found that whilst an increased administration of non-colloid fluid may increase the urinary output in those less extensively burned, it did not increase the output when the burns were very extensive

Few observations have been related to glomerular filtration or blood volume estimates and much remains to be done Recent studies indicate that glomerular filtration as measured by serial estimates of the endogenous creatinine and inulin clearances is often not closely related to the rate of flow of urine (Graber and Sevitt, 1957) In extensively burned patients treated by plasma and blood transfusion there is often a reduction in glomerular filtration, the degree of which may vary from hour to hour, whilst this is not necessarily reflected in the variations in the output of urine In the extreme case a *reduced*

temporary restoration of the blood volume whilst the subsequent fall in excretion is due to recurrence of oligaemia

Changes in the sodium chloride ratio as well as the amounts of ammonium bicarbonate and phosphate present influence the degree of acidity or alkalinity of the urine There is a tendency in many patients for the urinary pH to rise 2–6 days after burning when it may even become alkaline this may be related to the increased excretion of sodium relative to chloride partly through the influence of sodium citrate in the transfused plasma

Relationship to plasma levels—When fluid and electrolyte therapy is adequate the fall in the plasma sodium and chloride is only slight or moderate and usually to the lower limit of normal (Chapter 10) Therefore the plasma urine concentration ratios are raised and may be quite high This means that the suppression in the urinary excretion of sodium and chloride is an active retention and not the result of the plasma level falling below the renal threshold as postulated by Davidson (1926) and supported by Keyser (1948) When sodium diuresis commences the plasma sodium level returns to normal occasionally it may be slightly raised

WATER AND SALT DIURESIS

The reduction in the flow of urine is followed by an increased output which takes place about 3–6 days after burning and is related to the absorption of the burn oedema. The flow may be polyuric particularly when there has been a considerable positive balance of water but it is sometimes within the normal limits The release of water is usually associated with a sudden increase in the concentration and total excretion of sodium and chloride and this is maximal about 4–6 days after burning. Sometimes the water and salt diuresis are not quite in step more water than salt is initially excreted and this may account for the occasional rise of the plasma sodium and chloride

POTASSIUM EXCRETION

Unlike sodium the excretion of potassium is not restricted after burning. It is freely excreted but this does not mean that it is actively mobilized from the tissues The output is variable, is of the order of 40–90 milli-equivalents per day and is largely dependent on intake The daily excretion is often fairly steady and bears little relationship to the area burned or to the volume of urine passed During the first few days a moderate negative potassium balance occurs due to low intake but a positive balance is easily achieved by a moderate increase

largely determined by the amount of salt administered because the urine excretion is limited and only slightly altered by the intake

Recent observations have shown that the retention of sodium and chloride is not restricted to those with undamaged kidneys but is also a common (almost regular) event in patients who develop renal failure with azotaemia, whether the urine output is normal or whether severe oliguria occurs (Chapter 14)

Sodium relative to chloride excretion —The degrees of sodium and chloride retention and excretion are not necessarily parallel and the present evidence indicates that the ratio of sodium to chloride in the urine is influenced by (1) the greater retention of sodium in the oedema fluid, (2) the relative amounts in the intake, (3) the blood volume and (4) possibly the excretion of lactate and other organic acids Relatively more sodium than chloride is deviated into the burn oedema (as in normal extracellular fluid) and consequently less sodium than chloride is available for excretion during the period of electrolyte retention This can cause the sodium chloride ratio (calculated in equivalent values) to fall to 1 2 or less if the intake is restricted to fluids containing equimolecular proportions Later on more sodium than chloride is mobilized from the burn oedema for excretion and the sodium chloride ratio will rise and exceed unity

The pattern of excretion of sodium in patients treated with intravenous plasma often varies considerably from that of chloride during the first few days Cycles of change lasting a few hours may occur within the general phenomenon of sodium and chloride retention This has been established by examining serial (often hourly) samples of urine over a period of a few days (Graber and Sevitt, 1957) The excretion of chloride may fall before that of sodium and the patient then goes through a phase of some hours during which an extremely low urinary output of chloride is associated with a relatively normal excretion of sodium Examination of serial hourly samples has also shown that later on the excretion of sodium and chloride are not necessarily parallel Phases of increased excretion of sodium may occur whilst the urinary chloride remains low and the ratio of sodium to chloride in the urine in equivalent values may rise to between 5 1 and 20 1 The cause of this is unclear The additional sodium in citrated plasma can only account for a small part of the difference between the sodium and chloride excreted Part of the difference may also result from the presence of organic acids excreted as sodium salts but this explanation also is not adequate There is some suggestion that the phases of increased sodium excretion are related to

cell mass is not taken into account (Chapters 10 and 15) On the other hand Hardy and his colleagues (1955) reported that oliguria after burning did not necessarily reflect a diminished cardiac output since a reduced urinary output occurred when the blood pressure was normal and when the cardiac output was low normal or even raised

Adrenocortical hyperactivity—Hypersecretion of the adrenal cortex rapidly develops in burned patients (Chapter 18) and because certain adrenal hormones like aldosterone and hydrocortisone promote salt and water retention and potassium excretion some workers have concluded that the increased secretion of adrenal hormones determines the changes in electrolyte and water excretion (Thorn 1951, Moore 1951) It may be however that adrenal hormones play a permissive rather than a determining role in regulating the renal excretion of sodium chloride and potassium The permissive concept of adrenal function arose from observations on carbohydrate and nitrogen metabolism (Chapter 17) It is supported by the observations that post-operative sodium retention and potassium excretion take place in patients subjected to hypophysectomy or bilateral adrenalectomy when they were maintained on a constant dose of ACTH or cortisone respectively (Mason 1955 Graber and Beaconsfield, 1955)

Posterior pituitary gland.—It may be argued that secretion of antidiuretic hormone occurs after burning and is partly responsible for the oliguria Using a method for the isolation of antidiuretin Baar (1956) fractionated a peptide from the urine of burned patients but found that it had little antidiuretic activity in rats Even if the posterior pituitary were hyperactive it is probably not essential for the oliguria because Barac (1951a) showed that previous hypophysectomy in dogs did not suppress the antidiuretic effect of burning

Nervous and other humoral influences.—The experiments of Barac (1946) indicated that stimulation of the renal nerves could be incriminated in the rapid onset of oliguria When one kidney of a dog was previously denervated or transplanted into the neck burning the animal did not produce oliguria in the experimental kidney although the urine flow from the intact kidney rapidly fell Subsequent experiments showed that the protective effect of renal denervation could be overcome by *increasing* the renal blood flow (Barac, 1948 1951b) The flow of urine from the transplanted kidney was *reduced* after burning when the blood flow through the organ was enhanced This indicated that a blood borne factor could be responsible for oliguria and was more powerful in effect than nervous stimulation of the kidney

in intake The fall in the sodium excretion during the phase of retention results in a low sodium potassium ratio in the urine

PATHOGENESIS

The periods of retention and diuresis of water and sodium chloride closely correspond to the times of formation and reabsorption of the oedema and clearly indicate a close physiological connexion On the other hand this may not be the whole picture because (1) variations in the intake of fluid or salt during the phase of retention are merely followed by a fractional change in excretion, and (2) a similar retention occurs after injury or operation This suggests that there is an 'obligatory' retention of water and salt

The body mechanisms which produce the salt and water retention are only partly understood The factors involved include (1) low blood volume (2) humoral and nervous influences

Oligaemia—This is the most important single factor producing a fall in the urinary output Its effect is augmented when the blood pressure falls but oliguria and salt retention occur when the blood pressure is normal Profound oliguria may be classified into reversible and irreversible oliguria according to the effect of transfusion The oliguria is reversible when the blood volume is adequately increased by intravenous transfusion but it is irreversible when transfusion has little or no effect The pathogenesis of irreversibility is poorly understood but the main influences are a considerable and prolonged oligaemia and frank haemoglobinuria, whilst the mechanism appears to be a persistent reduction in glomerular filtration (Chapter 14)

The manner whereby oligaemia produces reversible oliguria is also rather obscure Renal vasoconstriction, posterior pituitary and adrenocortical stimulation and renal nervous stimulation have all been postulated

The importance of oligaemia is supported by the work of Flear and Clarke (1955) in the analogous field of trauma They showed that the adequacy of early blood transfusion modifies the excretion of electrolytes as well as water Retention of sodium and water did not occur *in injured patients receiving early or adequate transfusion* of blood but did occur in those who were not transfused This supports the contention of Borst (1948), Cort (1955) and others who stress the importance of blood volume, baroreceptors and nervous stimulation on renal function The findings of Flear and Clarke suggest that undercorrection of oligaemia in burned patients may be responsible for the water and salt retention This could arise from underestimation of oligaemia by blood haematocrit or haemoglobin observations if the simultaneous disappearance of part of the red

add further potassium but the adequacy of renal function by blood urea or other estimations should be ascertained before therapy of this kind is started

REFERENCES

Anderson, A. B., and Semeonoff E. (1945) In *Studies of Burns and Scalds* p 166, M R.C. Special Report Series No 249
Baar S (1956) *J clin. Path* 9 144
Barac, G (1946) *Compt rend Soc biol* 140 580 1107 1125
— (1947) *Ibid.*, 141 952.
— (1948). *Arch. intern Physiol Liège*, 56, 172.
— (1949). *Compt rend. Soc biol* 143, 550, 988 990
— (1951a) *Arch intern. Physiol Liège*, 58, 465
— (1951b) *Journées Therap Paris*, p 327
— (1952) In *Proc 6th Internat Cong Comparat Pathol Madrid* 357
— (1953) *Arch intern. Physiol Liège* 61 400 403 407 411
Borst, J G G (1948) *Acta med. Scand. Suppl.* 207
Bull, J P and England, N W J (1954) *Lancet* 2, 9
Cope, O and Moore, F D (1947) *Ann Surg.*, 126, 1010
Cort, J H (1955) *Physiol Bohemoslovenica*, 4 14
Davidson, E. C. (1926) *Arch Surg.*, 13, 262.
Flear C. T G and Clarke, R. (1955) *Clin Sci.*, 14, 575
Fox, C. L. (1944) *J Amer med. Ass.*, 124 207
Graber I G and Beaconsfield, P (1955) *Brit med J.*, 2, 704
— and Sevitt, S (1957) Unpublished observations.
Hardy J D., Neeley W A. Wilson, F C Lovelace, J R., and Jabbour E. (1955) *Surg Gynec Obstet* 101 94
Keyser J W (1948). *Ann Surg* 127 605
Markley K., Bocanegra, M Bazan, A Temple R. Chiappori, M., Morales, G and Carrion, A. (1956) *J Amer med. Ass.*, 161 1465
Mason, A S (1955) *Lancet* 2, 632.
Moosalngeon, A. (1949) *Semaine des Hopitaux* 79 1
Moore F D (1951) In *Symposium on Burns* p 106 Washington National Research Council.
— and Ball, M R (1952) *Metabolic Response to Surgery* Springfield Thomas.
Pack G T (1926) *Arch. Path. Lab Med.*, 1 767
Thorn, G W (1951) In *Symposium on Burns* p 97 Washington National Research Council.

Although the humoral nature of post-burn oliguria has been stressed by Barac many of his other results can be explained by oligaemia In cross-circulation experiments between a burned and an unburned dog oliguria rapidly developed in the burned and unburned animals (Barac, 1946), oligaemia could have been responsible for this and not the cross-circulation of a humoral factor as postulated In other experiments oliguria was not prevented by previous denervation of the burned skin, but if the blood supply to the skin was cut off a few seconds before burning, the subsequent urine flow was not reduced (Barac, 1949, 1951b), again this procedure would have prevented burn oedema and oligaemia The origin and nature of the postulated humoral factor was not discovered but certain experiments indicated that it could not be adrenaline or histamine (Barac, 1947, 1949) whilst it could be a substance liberated from heated red cells during intravascular haemolysis (Barac, 1952) Whilst investigating the possible role of 5-hydroxy-tryptamine this worker found that the oligurias produced by this compound and by burning were relieved by the intravenous injection of large amounts of ascorbic acid (Barac, 1953)

CLINICAL IMPLICATIONS

The role of oligaemia in the production of oliguria after burning is clear, and intravenous colloid therapy should be directed to maintaining a near-normal blood volume (*see* Chapter 10)

However the apparent obligatory reduction in the urine flow during the first few days should not be mistaken for renal failure and the patient should not be overloaded with fluid in order to maintain a "normal" urinary output In an adult a urine flow of 0 5–1 0 litre per day during the shock period may be accepted as a satisfactory compromise and an hourly rate below 25 millilitres as inadequate Notwithstanding, the rate of excretion of urine does not often reflect the adequacy of renal function and a normal excretion of urine may be associated with a progressive azotaemia and renal failure (*see* Chapter 14)

Salt should not be given in excess of water because of the danger of increasing and prolonging the oedema The amounts of sodium, chloride and other ions which are administered to extensively burned patients vary widely from centre to centre and there is as yet no exact knowledge of the optimum amounts required

The free excretion of potassium should be ignored unless the patient develops a significant hypopotassaemia, when the administration of potassium salts is indicated If feeding with a milk-egg mixture is commenced on the second day there is usually no need to

tubular necrosis (*vide infra*) was found On the other hand if the patient survives more than 4 or 5 days considerable azotaemia is found uraemia with acidaemia develops and contributes to death The serum levels of potassium and phosphate increase considerably and the serum calcium falls For example a girl aged 9 years with 55 per cent body area burns passed 130 137 69 5 and 4 millilitres of urine on successive days her blood urea rose from 160 milligrams per 100 millilitres on the third day to 318 milligrams on the fifth day when she died Her serum potassium and phosphate values rose to 37 and 9 2 milligrams per 100 millilitres respectively and the sodium and calcium levels fell to 278 and 7 7 milligrams per 100 millilitres respectively At autopsy the later developed stage of distal tubular necrosis was found Burned patients who survive anuric renal failure have not been described Should recovery occur it would probably be heralded by a period of diuresis such as occurs with recovery from acute anuria from other causes

Uraemia with little or no oliguria —Attention has recently been drawn to this form of acute renal failure (Sevitt, 1956a) Considerable azotaemia and uraemic symptoms develop in recently burned subjects in whom oliguria is slight, transient or absent For example a woman aged 35 years with 40 per cent body area burns passed 650 millilitres of urine during the first 24 hours 1–2 litres daily thereafter and died on the twelfth day The blood urea level rose from 232 milligrams per 100 millilitres on the seventh day to 420 milligrams and she died in uraemia with bronchopneumonia diffuse distal tubular necrosis was found at autopsy The non-oliguric form of acute uraemia is important to recognize clinically because the patient s chance of survival may have increased with recent advances in therapy Both Shen Ham and Fleming (1943) and Goodpastor and his colleagues (1946) made passing reference to similar cases among their fatally burned subjects That the syndrome is not restricted to burned patients is illustrated by the fact that Luetscher and Blackfan (1943) described apparently similar cases produced by sulphathiazole, Smith (1951) refers to two seriously injured patients studied by Burnett and his colleagues at the Italian front who may belong to this category Teschan and his colleagues (1955) described cases of post traumatic uraemia without oliguria after battle wounds and Sevitt s description included one post traumatic case

MORPHOLOGICAL CHANGES

Terminology and classification.—Lucké (1946) coined the term lower nephron nephrosis because the histological lesions mainly affect the distal tubules but this term is unsuitable since tubular necrosis

CHAPTER 14

RENAL FAILURE AND TUBULAR NECROSIS

INTEREST in acute post-traumatic renal failure was stimulated by the reports of "crush anuria" resulting from the air raids on Great Britain during the last war (Dunn Gillespie and Niven, 1941, Bywaters and Beall 1941, Bywaters and Dible, 1942) A similar clinico-pathological syndrome occurs after other severe injuries, abortion incompatible blood transfusion, sulphonamide intoxication and in many other conditions including extensive burns Clinico-pathological descriptions of renal failure following burns have been given by Christophe (1939), Shen, Ham and Fleming (1943), Goodpastor and his colleagues, (1946) Sevitt (1956a, 1956b), and Lucke (1946) in his analysis of 538 fatal cases included 48 burned subjects Histological accounts of renal changes in burned patients have also been reported by Pack (1926), Vogt (1929), Zinck (1940), Erb Morgan and Farmer (1943), Gibson (1945), Martineau and Hartman (1947) and many older writers Unfortunately few renal function studies have been made

CLINICAL TYPES OF ACUTE RENAL FAILURE

Two main kinds of renal failure occur oliguric and non-oliguric All patients concerned are extensively burned, usually more than 30 per cent of the body area is involved, and deep haemoglobinuria is frequent

Severe oliguria or anuria —This is the classical variety described by all writers Soon after burning the flow of urine rapidly falls and anuria or severe oliguria develops The latter was defined by Bull, Joekes and Lowe (1950) for other kinds of acute oliguria as the excretion of not more than 300 millilitres of urine per day and usually considerably less The urine deposit in the burned patients generally contains numerous brown-pigmented granular casts, Prussian-blue-positive granular fragments, epithelial cells, a few red blood cells and is strongly benzidine-positive Many patients die during the first 2 or 3 days from causes unrelated to renal failure and before uraemia has time to develop For example a boy aged 12 years suffered burns on 45 per cent of the body area, passed 160, 40 and 20 millilitres of urine in successive 12-hour periods in spite of plasma transfusion, and died 36 hours after burning in acute respiratory distress associated with congestive atelectasis At autopsy the early form of diffuse distal

granular casts which stain pink or deep red in the picromallory preparations, are also benzidine positive and parts of the casts often stain positive by the periodic acid Schiff technique, possibly because muco- or glyco-proteins are present Albuminous exudate and cellular debris are often mixed with the casts and may be present in many other tubules Early tubulo-epithelial necrosis is common in tubules distended by casts and is usually focal It is manifest by local thinning and eosinophilic staining of the cytoplasm and nuclear pyknosis (Fig 49) Necrosis of Henle tubules free from casts is unusual but appears as foci of granular cytoplasmic disintegration with nuclear lysis In a few patients small foci of necrosis affect the proximal convoluted or descending tubule By microdissection of individual nephrons in histologically similar cases of varied aetiology Oliver and his co-workers have shown that the tubular necrosis may be widespread and involve foci of the proximal as well as the distal tubule (Oliver MacDowell and Tracy 1951 Oliver 1953) but in burned patients necrosis mainly affects the distal tubule

In addition there is often a widespread pale appearance of the proximal convoluted tubules due to a loss of eosinophilic staining (Sevitt, 1957) The nuclei are in the basal position and the eosinophilic cell borders are thickened and prominent as if the normal cytoplasm was compressed by abnormal contents Close examination reveals a sparse fine eosinophilic structure to the empty looking cytoplasm the appearance of which may result from the solution during processing of a cytoplasmic substance A similar change was reported by Brun (1954) in the kidneys of patients with renal failure due to causes other than burning, and the appearance is not dissimilar to that seen in experimental animals after the parenteral administration of sucrose Sometimes the first part of the proximal convoluted tubule particularly the neck contains many coarse eosinophilic hyaline cytoplasmic granules which stain red by the periodic acid Schiff method their nature is unknown but they are not glycogen or dextran The significance of these proximal tubular changes is uncertain but they may be related to the metabolic effects of burning or to therapy rather than to renal failure

Glomerular changes also occur The capsules commonly contain albuminous debris and coarse eosinophilic granules about the size of red cells these may arise from desquamated cells of Bowman s parietal layer or as Burwell (1955) suggested, from the cervical origin of the proximal convoluted tubules Frequently the glomerular tuft contains numerous fine fat globules about 1 μ in diameter Histologically they are situated outside the capillary lumen and involve the capillary endothelium and possibly the glomerular

is the essential morphological feature (Oliver, MacDowell and Tracy, 1951, Bull and Dible, 1953)

In his analysis of 86 fatally burned patients Sevitt (1956b) found that the renal histological picture in 34 subjects was similar to lower nephron nephrosis whilst an extensive necrosis of the proximal tubules was present in 17 others He divided the histology of acute renal failure after burning into (1) distal tubular necrosis, and (2) proximal tubular necrosis

When distal tubular necrosis is widespread, affecting many nephrons, it is called *diffuse* distal tubular necrosis, and the picture is associated either with anuria or severe oliguria or with the non-oliguric form of acute uraemia Diffuse distal tubular necrosis occurs at all ages but is most common in children and young adults

When distal tubular necrosis affects few nephrons it is called *focal* distal tubular necrosis Most of the affected are children, those who die succumb to causes generally unrelated to uraemia and many probably survive but a minority develop reversible or irreversible renal failure The terms diffuse and focal refer to the histological density of lesions but in both kinds the tubules are affected in a discrete or focal fashion

Proximal tubular necrosis mainly occurs in elderly subjects who have nephrosclerosis Most of them develop oliguria and die within a few days of burning with a rising blood urea concentration The burns are extensive but generally less than found in patients with distal tubular necrosis For example a woman aged 60 years sustained burns of 28 per cent of the body area and died 3 days later She passed 1,100, 330 and 170 millilitres of urine on successive days and her blood urea rose to 110 milligrams per 100 millilitres At autopsy nephrosclerosis and proximal tubular necrosis were found Occasionally non-oliguric renal failure occurs

Diffuse distal tubular necrosis (lower nephron nephrosis) —The changes depend on the duration of survival

Early stage —This is found among those who die during the first 2 or 3 days At autopsy the kidneys are moderately or deeply congested and may drip blood from the cut surface Histologically the prominent feature is the presence of numerous haemoglobin and granular eosinophilic casts in many collecting and wide Henle tubules (Fig 49), these also occur frequently in second convoluted tubules but rarely in the proximal tubules, the casts often distend the tubules and may appear to block them Many are amorphous fused masses of haemoglobin, others are granular Occasional intratubular groups of red cells are present but are not a feature Many of the eosinophilic

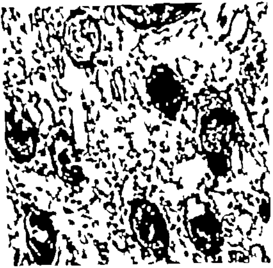


FIG 50—Many tubules in the pyramid are distended by haemoglobin casts. Death 4–5 days after burning. (Haematoxylin and eosin × 140)

repair by spreading and regeneration of thin epithelium is present and produces peculiar tubular forms including plicated or concertina like folds and double or treble layers of epithelium between the casts and the basement membrane Interstitial oedema and collections of inflammatory cells are found around many straight and distal convoluted tubules particularly those ruptured or blocked by casts Lymphocytes predominate and some plasma cells may be present with perhaps a few polymorphs and eosinophil leucocytes. Cellular collections are also seen around venules in the boundary zone and elsewhere Evidence of tubular rupture into venules is present Mural thrombosis of venules is not uncommon and some thrombi may be surrounded or invaded by a layer of tubular epithelium which

FIG 51—Thrombosis of a vein in the boundary zone of the cortex Early organization is present and a thin layer of regenerating tubular epithelium has spread around part of the clot. This indicates former tubulo-venous anastomosis. Death 10 days after burning. (Haematoxylin and eosin × 150)

epithelium Sometimes the globules are so numerous that some of the cells of the tuft have a foamy appearance in paraffin sections Many glomeruli are hyperaemic but some tufts and the related peritubular network are often ischaemic Glomerular capillary thrombosis is discussed later

Later stage —The kidneys are enlarged and swollen and the capsules are tense the cortices are widened and often pale in contrast with the red striated pyramids The cortical markings are ill defined, the parenchyma may be softer than usual, and minute greyish-white

FIG 49 —Many Henle tubules in the boundary zone of the cortex contain haemoglobin casts and parts of the tubular epithelium are thinned and necrotic Death 48 hours after burning (Haematoxylin and eosin, × 225)

(cellular) foci are often visible particularly at the bases of the pyramids

Histologically the picture of distal tubular necrosis is more advanced The characteristic changes are (1) casts and discrete tubular necroses in the distal and collecting tubules (Fig 50) particularly in the boundary zone of the cortex, (2) fatty change in most of the distal tubules, (3) tubulo-epithelial regeneration, (4) tubulovenous anastomoses and venous thrombi (Fig 51) and (5) interstitial oedema and an inflammatory cellular exudate In most patients many of the casts obviously contain haemoglobin, but in a few subjects few or none of the casts are benzidine-positive and only granular eosinophilic, colloid or albuminous casts are found In such patients haemoglobinuria was not reported Attempts at tubular

FIG 52.—An occasional Henle tubule is distended by a haemoglobin cast. The epithelium of this tubule is irregularly necrotic. Death 16 hours after burning. (Haematoxylin and eosin 210)

FIG. 53 —One of the few focal collections of lymphoid cells which lies near a distal convoluted tubule dilated by a cast. Note the newly spread epithelium which lines this and other parts of the distal tubule Death 35 days after burning. (Haematoxylin and eosin × 180)

regeneration may be found Focal collections of lymphoid cells are seen around some of these tubules and/or around venules (Fig 53) Occasionally these are thrombosed and organization is in progress Essentially the morphological picture is similar to that seen in the diffuse form except that few tubules are involved

The main morphological changes which are believed to represent the healing stage or the healed residue of a recent focal attack consist of characteristically situated focal collections of lymphoid cells and occasional organizing venous thrombi particularly in the boundary zone A few haemoglobin or granular casts may be found direct evidence of tubular necrosis or regeneration of epithelium may be seen and small scattered calcified tubular foci may be present The term "healing is applied when tubular evidence of necrosis or

has spread into the vein from a nearby ruptured and regenerating tubule (Fig 51) Organization of the clot also occurs Epithelial regeneration and interstitial inflammatory changes are generally more advanced in those who survive longer

The parietal layer of many Bowman's capsules is often cubical or even low-columnar as if over-vigorous replacement of previously desquamated epithelium had occurred Some cloudy swelling and albuminous exudate is not infrequent in the proximal tubules and the pale cytoplasmic change and eosinophilic hyaline droplets may be present (*vide supra*) Another feature is the presence of many unusual mononuclear cells within the venules of the pyramid As Dible (Bull and Dible 1953) stated, they appear similar to many bone marrow cells and he suggested that they arise from the vascular endothelium as a result of stagnation of the venous flow The cells are seen in both oliguric and non-oliguric forms; indeed no histological difference between these clinical varieties of diffuse distal tubular necrosis are distinguishable

Focal distal tubular necrosis.—Nearly all the patients with this condition are children with extensive burns but few of them develop renal failure The urinary output is normal, little or no azotaemia occurs and when the patient dies the cause is generally unrelated to uraemia or renal failure Occasionally oliguric or non-oliguric uraemia develops but is sometimes associated with severe degeneration of the proximal tubules A number of patients go through a phase of reversible azotaemia followed by normal kidney function

The histological appearance varies with the duration of survival

Early stage.—This is found in those who die within 48 hours Although most have had frank haemoglobinuria nevertheless only a few scattered granular or amorphous haemoglobin and eosinophilic casts are seen in a few collecting ascending Henle and distal convoluted tubules (Fig 52) The density of casts varies but is rarely more than 1 or 2 per low-power field and is often less Most of the tubules do not contain casts and appear normal Early discrete pyknonecrosis of tubules is generally restricted to some of those blocked by casts but occasionally necrosis of tubules without casts is present

Later stages.—The kidneys of those who survive longer may be subclassified into "active", "healing" and "healed" types The "active" form is characterized by a few casts of different kinds namely haemoglobin, granular eosinophilic and occasionally only colloid casts (Fig 53). The epithelium of the distended parts of the tubules is usually thin, a few localized necrotic foci are present and tubular

Evidence of cortical ischaemia is usual but may be focal and irregular and affect only the peritubular capillary networks glomerular ischaemia is sometimes a feature

Casts are found in many cases Mostly they are of the kind commonly found in nephrosclerotic kidneys but often some containing haemoglobin are found in the second convoluted or distal tubules Such casts are not numerous but in a few cases the appearance is suggestive of co-existent distal tubular necrosis

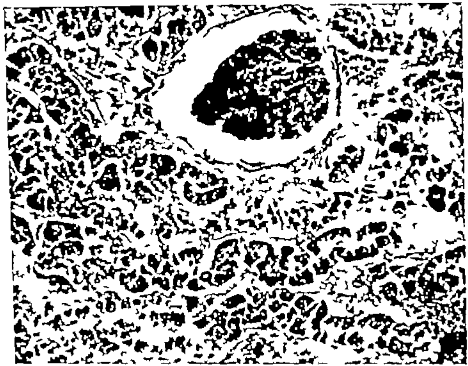


FIG 54 —Cortex of kidney showing proximal tubular necrosis. (Haematoxylin and eosin × 210)

Nephrosclerotic atrophy and focal fibrosis of the cortex is found in most of the kidneys but it is not invariable sometimes a hyaline change affects afferent glomerular arterioles The significance of nephrosclerosis will be considered later

Glomerular capillary thrombi.—Thrombi within glomerular capillaries of burned patients were reported by Wertheim (1867) and were seen in about 10 per cent of the subjects reported by Sevitt (1956b) Histologically they often block and distend many capillaries in a single tuft they are rarely seen in the afferent arterioles Their number and extent vary considerably sometimes more than half the glomeruli are affected and in others only an occasional capillary of a

regeneration persists, the term "healed" is applicable when there is no tubular evidence of tubular necrosis except the calcified spots In these kidneys the characteristically located lymphoid cell collections and occasionally an organizing venous thrombus are the residue of a focal distal tubular necrosis The interstitial cellular foci may lead to a diagnosis of interstitial nephritis if the entire histological process is not considered It may be that some cases diagnosed histologically as interstitial nephritis because of focal collections of lymphoid cells, like those described by Martineau and Hartman (1947), are in reality the healed or healing residue of distal tubular necrosis

Proximal tubular necrosis—A generalized cortical pallor of the kidneys is frequent, and after fixation in formol saline the cortex assumes a grey "necrotic" appearance In an occasional patient a number of paler more or less circumscribed cortical areas are surrounded by narrow red borders These ischaemic zones are restricted to the outer two-thirds of the cortex whilst the deeper cortex and medulla are congested This rather uncommon appearance is suggestive of the type of cortical ischaemia and medullary by-pass described by Trueta and his colleagues (1947) A similar appearance but with glomerulo-tubular necrosis was described by Brown and Crane (1943) in a fatally burned patient

Histologically the essential change is a widespread necrosis of the proximal convoluted tubules (Fig 54) The epithelial nuclei have either disappeared or are in a process of lysis The epithelial cells are often loosened from each other and from the basement membrane and sometimes they lose or tend to lose their tubular arrangement, but the peritubular membrane remains intact The extent of the tubular necrosis varies but is always considerable Often all or most of the tubules are affected, in many others about half the tubules are involved and in a few cases the necrosis is focal, perhaps semiconfluent but less extensive The second convoluted tubules often appear viable, but they are collapsed and often degenerate and are surrounded by a sea of obviously necrotic proximal tubules In the cortex many of the wide straight tubules are necrotic, but in the pyramids the collecting and Henle tubules are commonly viable although usually collapsed, empty and separated by oedema The glomerular tufts are often normal but in a few cases are also necrotic and small haemorrhages may be present

Subcapsular rims or zones of histologically viable cortex are found in most cases, the viability probably resulting from the blood supply through the independent renal capsular vessels

Evidence of cortical ischaemia is usual but may be focal and irregular and affect only the peritubular capillary networks glomerular ischaemia is sometimes a feature

Casts are found in many cases Mostly they are of the kind commonly found in nephrosclerotic kidneys but often some containing haemoglobin are found in the second convoluted or distal tubules Such casts are not numerous but in a few cases the appearance is suggestive of co-existent distal tubular necrosis

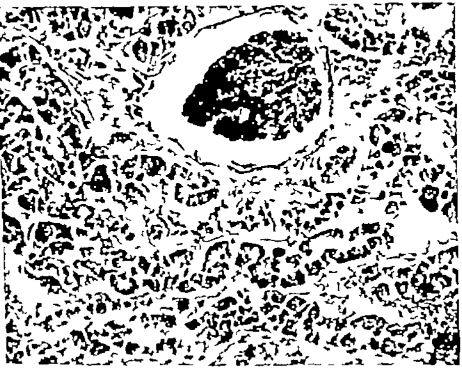


FIG. 54 —Cortex of kidney showing proximal tubular necrosis (Haematoxylin and eosin × 210)

Nephrosclerotic atrophy and focal fibrosis of the cortex is found in most of the kidneys but it is not invariable sometimes a hyaline change affects afferent glomerular arterioles The significance of nephrosclerosis will be considered later

Glomerular capillary thrombi—Thrombi within glomerular capillaries of burned patients were reported by Wertheim (1867) and were seen in about 10 per cent of the subjects reported by Sevitt (1956b) Histologically they often block and distend many capillaries in a single tuft they are rarely seen in the afferent arterioles Their number and extent vary considerably sometimes more than half the glomeruli are affected and in others only an occasional capillary of a

few tufts contain thrombi The condition is apparently not found in children and is most frequent in elderly people who die with distal or proximal tubular necrosis during the second day after burning, it is rare before or after the second day The thrombi are probably embolic in origin and result from the trapping of heat-precipitated fibrin and other microscopic debris within the glomerular capillaries They appear to be a temporary phenomenon since they are rarely seen in those who survive more than 2 days It is unlikely that they play a significant part in the pathogenesis of tubular necrosis

RENAL FUNCTION

Emphasis has been laid on tubular dysfunction and necrosis as the dominating lesion in acute renal failure, but the primary and initiating change appears to be a considerable reduction in the rate of glomerular filtration This is not to underestimate the importance of tubular changes but these seem to follow and maintain the renal impairment rather than produce it

Glomerular filtration and azotaemia —Serial estimations of the endogenous creatinine and urea clearances during the first and subsequent days after burning have shown a considerable reduction in the clearance values in patients who develop either oliguric renal failure or azotaemia without oliguria (Graber and Sevitt, 1957) If the creatinine clearance values can be equated with glomerular filtration rate (G F R) the results indicate a serious fall in the G F R The interpretation of clearance tests in patients with tubular damage is open to criticism because the low results may be due to unselective back-diffusion or reabsorption by the tubules of water and solutes which tubular damage could permit (Phillips and Hamilton, 1948), and indeed Lucké (1946) suggested that unselective tubular reabsorption was the cause of post-traumatic uraemia On the other hand in burned patients the fall in the urea and creatinine clearance values often occurs quickly and sharply and within a few hours of extensive burning the values may be only 5–10 per cent of normal It appears unlikely that serious tubular impairment could be responsible at this stage for the low clearance values, although later on tubular damage could contribute

The fall in the G F R is accompanied by a progressive rise in the levels of the serum urea and creatinine either when severe oliguria is present or when the urine flow is within normal limits Low filtration is particularly likely when fluid therapy is delayed or poor but it is not an infrequent phenomenon even in patients who are adequately transfused with plasma at an early stage Indeed restoration of the blood volume to normal a few hours after burning may or may not

be accompanied by an increase in the G F R and in the latter event severe oliguric failure or azotaemia without oliguria often develops The manner and duration of the fall in the G F R varies Sometimes the fall is early and precipitous very low values are obtained and the reduced rate may continue until death occurs in uraemia or from other causes Alternatively the low early filtration rate is temporary and is restored to normal or near normal within a day or two in such patients azotaemia develops during the first few days but it is reversible and the blood urea and serum creatinine values return to normal In other patients the fall in the G F R is gradual and is accompanied by a slowly progressive azotaemia Finally even in patients who fail to develop azotaemia and who show no evidence of renal impairment there may be a temporary perhaps intermittent reduction in the G F R during the first day or two with subsequent return to normal These findings are supported by the work of Dzie mian (1948) in extensively burned goats He also found a fall in the G F R which occurred either sharply or gradually and progressively and was not apparently influenced by blood or plasma transfusion The effective renal plasma flow was considerably reduced more than the fall in G F R so that the filtration fraction was increased This indicated in the view of this worker constriction of the efferent glomerular arterioles The experience of Haynes DeBakey and Den man (1951) underestimates the incidence or importance of acute renal failure in treated patients Eight patients were studied by them the G F R was found to be raised renal plasma flow was within normal limits tubular function appeared to be unimpaired, and they concluded that renal function in adequately transfused patients is compatible with complete recovery Their uniformly fortunate experience may be a chance phenomenon

Tubular function.—There is a curious paradox between the failure of the tubules to reabsorb water and their considerable efficiency in reabsorbing sodium and chloride (Sevitt 1956b Graber and Sevitt 1957) If the urine volume V is expressed as a percentage of G F R $\left(\frac{UV}{P}\text{ creatinine}\right)$ it becomes apparent that the percentage of the filtrate excreted into the bladder $\left(\frac{P}{U}\text{creatinine} \times 100\right)$ is considerably greater than the normal 1 per cent or so and the amount passed may rise to 10 per cent or even 20 per cent of the glomerular filtrate This is particularly evident in patients in whom azotaemia develops without oliguria but high values are also found in patients with considerable oliguria Evidently the volume of the urine flow in these cases is largely dependent on the reduced absorption of water by the tubules

few tufts contain thrombi. The condition is apparently not found in children and is most frequent in elderly people who die with distal or proximal tubular necrosis during the second day after burning; it is rare before or after the second day. The thrombi are probably embolic in origin and result from the trapping of heat-precipitated fibrin and other microscopic debris within the glomerular capillaries. They appear to be a temporary phenomenon since they are rarely seen in those who survive more than 2 days. It is unlikely that they play a significant part in the pathogenesis of tubular necrosis.

RENAL FUNCTION

Emphasis has been laid on tubular dysfunction and necrosis as the dominating lesion in acute renal failure, but the primary and initiating change appears to be a considerable reduction in the rate of glomerular filtration. This is not to underestimate the importance of tubular changes but these seem to follow and maintain the renal impairment rather than produce it.

Glomerular filtration and azotaemia.—Serial estimations of the endogenous creatinine and urea clearances during the first and subsequent days after burning have shown a considerable reduction in the clearance values in patients who develop either oliguric renal failure or azotaemia without oliguria (Graber and Sevitt, 1957). If the creatinine clearance values can be equated with glomerular filtration rate (G.F.R.) the results indicate a serious fall in the G.F.R. The interpretation of clearance tests in patients with tubular damage is open to criticism because the low results may be due to unselective back-diffusion or reabsorption by the tubules of water and solutes which tubular damage could permit (Phillips and Hamilton, 1948), and indeed Lucke (1946) suggested that unselective tubular reabsorption was the cause of post-traumatic uraemia. On the other hand in burned patients the fall in the urea and creatinine clearance values often occurs quickly and sharply and within a few hours of extensive burning the values may be only 5–10 per cent of normal. It appears unlikely that serious tubular impairment could be responsible at this stage for the low clearance values, although later on tubular damage could contribute.

The fall in the G.F.R. is accompanied by a progressive rise in the levels of the serum urea and creatinine either when severe oliguria is present or when the urine flow is within normal limits. Low filtration is particularly likely when fluid therapy is delayed or poor but it is not an infrequent phenomenon even in patients who are adequately transfused with plasma at an early stage. Indeed restoration of the blood volume to normal a few hours after burning may or may not

nephrosclerosis predispose to proximal tubular necrosis when oligaemia is present. Focal distal tubular necrosis appears to result when oligaemia is moderate and haemoglobinuria is absent or when haemoglobinuria occurs but persistent oligaemia is prevented at an early phase

Oligaemia and renal ischaemia.—Oligaemia is a universal event after extensive burning, largely from loss of plasma and partly from loss of red cell mass (Chapters 10 and 15) If the urine flow is to be maintained the blood volume must be kept within certain limits and as near normal as possible If transfusion of plasma is delayed or inadequate the flow of urine decreases and may even cease, but it can often be restored by increasing the rate of transfusion The minimal duration and depth of oligaemia necessary to produce renal failure are not known with certainty but clinical experience indicates that oliguric or non-oliguric failure is likely to develop when a blood volume below 70 per cent of normal persists for 2–4 hours or longer—but of course there are many individual variations

Various workers have found that oligaemia greatly reduced the blood flow through the kidneys The experiments in dogs by Van Slyke and his colleagues (1944) indicated that haemorrhagic and traumatic oligaemia were followed by a great reduction both in renal blood flow and in urine secretion and similar findings were reported in man by Lauson Bradley and Cournand (1944) and in cats by Keele and Slome (1945) The reduction in renal blood flow was not due to hypotension was much greater than the fall in the cardiac output and was attributed to renal vasoconstriction Few studies have been made after burning in burned goats Dziemian (1948) found a considerable reduction in the renal plasma flow which was reduced more than the glomerular filtration rate The renal clearance studies by Lauson Bradley and Cournand (1944) included one extensively burned patient who showed a considerable reduction in the renal blood flow whilst the adequately transfused burned patients with a urine flow above 100 millilitres per hour reported by Haynes DeBakey and Denman (1951) had normal renal blood flows on the second day after burning or later

Studies of the renal blood flow in patients with oliguric or non oliguric renal failure after burning have not yet been reported but it is likely that they are considerably reduced

Changes following temporary clamping of the renal artery.—Renal clamping experiments indicate that proximal tubular necrosis could result from prolonged renal ischaemia In unilaterally nephrectomized animals the remaining renal artery was temporarily clamped or

had the tubular reabsorption of water been normal the volume of urine would have been reduced in proportion to the reduction in the G F R The specific gravity and osmolarity of the urine remain low and the specific gravity is generally fixed at about 1 010 to 1 012 Relative failure of the tubules to reabsorb water had previously been noted by Bull, Jockes and Lowe (1950) in patients with oliguric renal failure from various causes It may be that the increase in the percentage of water excreted is physiological and compensatory to the reduced G F R rather than a selective pathological impairment of tubular function, since the tubules retain an uninhibited power to reabsorb sodium and chloride

The considerable tubular power to reabsorb sodium and chloride is revealed by the low urinary concentration and small daily output of these substances in the urine, particularly during the first few days after burning, in the presence of normal or near-normal plasma levels The $\frac{P}{U}$ ratios for sodium and chloride are therefore high, and the sodium excreted expressed as a percentage of the sodium filtered by the glomeruli is low at the same time as the percentage excretion of water is abnormally raised In this persistence of reabsorptive power for sodium and chloride the kidneys of burned patients with renal failure differ from those studied by Bull and his colleagues (1950) who found a free excretion of sodium and chloride during the oliguric and early diuretic phases Further studies of tubular function are required such as their ability to form and excrete hydrogen and ammonium ions and to reabsorb uric acid, phosphate, sulphate and other substances

PATHOGENESIS

A full explanation of renal failure and tubular necrosis must take into account the oliguric and non-oliguric forms of uraemia, glomerular and tubular function, the histological patterns of proximal and distal tubular necrosis and the relationship of these to various aetiological factors such as oligaemia and haemoglobinuria It is only possible to answer some of the questions raised The reduction in glomerular filtration is probably due to a reduction in the renal blood flow precipitated by oligaemia, worsened by hypotension and accentuated by renal vasoconstriction from oligaemia, haemoglobinaemia and probably other factors The tubular changes which dominate the histological picture appear to be secondary and sustaining influences from the functional point of view In general terms the combination of oligaemia and haemoglobinuria is responsible for diffuse distal tubular necrosis, whilst age and

outer major part of the cortex It is more likely to occur in nephrosclerotic kidneys because as Trueta and his colleagues demonstrated a direct communication exists between the afferent and efferent arterioles in the juxta medullary glomeruli after fibrous occlusion of most of the capillaries in the tuft This has relevance to proximal tubular necrosis after burning because most of the cases occur in elderly patients with nephrosclerosis The cortical by pass probably does not occur in kidneys which develop diffuse distal tubular necrosis because, among other evidence the renal arteriovenous differences for oxygen and carbon dioxide is normal in patients with anuric renal failure following incompatible blood transfusion (Barker Clark and Crossley 1950)

Studies of the intrarenal blood flow in burned animals have been made by Sevitt (1948) and by Monsaingeon Tanret and Daussy (1949) by the *in vivo* injection of colloidal dyes or suspensions Only multiple small ischaemic foci of irregular distribution were found by Sevitt whilst the majority of glomerular and peritubular capillaries were opened and hyperaemic but many of the animals of Monsaingeon and his colleagues (which were burned more extensively and for longer periods than those of Sevitt) showed either a total renal ischaemia or an ischaemia of the outer two-thirds of the cortex like that described by Trueta and his colleagues Thus the extent and severity of burning influences the renal vascular pattern

Nervous and humoral production of renal vasospasm —Reflex stimulation of the renal nerves could be responsible for the disturbance of the renal and intra renal blood flow because stimulation of the splanchnic nerves produces either total renal ischaemia or the by pass mechanism (Trueta and his colleagues 1947) The afferent path may be stimulated by baroreceptors in the blood vessels responding to changes in blood volume (Borst, 1948 Cort 1955) On the other hand a humoral substance may be implicated because Page (1943) found that the plasma of burned dogs developed vasoconstrictor properties for the vessels of the isolated rabbit s ear Intravascular haemolysis may also augment or induce renal vasoconstriction (*vide infra*) The relative values of the nervous and humoral mechanisms is not known but reflex vasospasm from oligaemia is probably more important

Origin of proximal tubular necrosis —The viable subcapsular rim of cortex in this condition suggests that the tubular damage results from ischaemic anoxia in the distribution of the main artery Taking the clinical histological and experimental evidence together it may be concluded that proximal tubular necrosis results from renal

ligated When the clamping in dogs was for 4–6 hours or longer the animals developed a progressive azotaemia and died within a few days (Van Slyke and his colleagues, 1944, Hamilton, Phillips and Hiller, 1948) Clamping for 3–4½ hours was followed by complete renal or a gross cortical necrosis (de Wardener, 1955) Lesser periods of clamping often produced reversible azotaemia and functional damage Release of the artery 20 minutes to 2 hours after clamping was followed by an immediate resumption of the renal blood flow, but there was evidence of functional tubular damage which was greater the more prolonged the clamping (Phillips and Hamilton, 1948) The rabbit kidney may be more susceptible to ischaemia Arterial clamping for 2 hours was followed by irreversible azotaemia, death within a few days and cortical tubular necrosis (Scarff and Keele, 1943, Badenoch and Darmady, 1947) Burwell (1955), who studied serial histological sections, found that the damage after clamping for 1½–4 hours mainly affected the descending medullary portion of the proximal tubule Badenoch and Darmady (1947) found that lesser periods of clamping (or partial clamping) produced a lower death rate and often a reversible azotaemia They claimed that the histological changes in such animals are comparable to those seen in human "traumatic uraemia" (diffuse distal tubular necrosis) but in view of Burwell's work it is likely that the descending part of the proximal tubule was affected and not the wide ascending limb of Henle

Unfortunately details of urine flow have not been reported in these experiments, but the urea clearance tests carried out by Hamilton, Phillips and Hiller (1948) indicate that secretion of urine did continue when the artery was released 2–3 hours after clamping It is possible that uraemia was accompanied by little or no oliguria in some of the animals and by severe oliguria in others

The period of ischaemia necessary to produce tubular damage in man is not known but the human kidney is not necessarily more resistant to ischaemia than the dog's Brun (1954) thought that 4–6 hours of renal vasoconstriction was necessary before ischaemic anuria occurred

Renal arterial by-pass —Trueta and his colleagues (1947) demonstrated an intrarenal vascular by-pass mechanism The blood for the distal two-thirds or three-quarters of the cortex is diverted through the juxta-medullary glomeruli, the efferent vessels of which loop downwards and drain directly into the tributaries of the renal vein The by-pass is brought about by vasospasm of the interlobular arteries and afferent arterioles which produces an ischaemia of the

outer major part of the cortex It is more likely to occur in nephrosclerotic kidneys because, as Trueta and his colleagues demonstrated a direct communication exists between the afferent and efferent arterioles in the juxta medullary glomeruli after fibrous occlusion of most of the capillaries in the tuft This has relevance to proximal tubular necrosis after burning because most of the cases occur in elderly patients with nephrosclerosis The cortical by pass probably does not occur in kidneys which develop diffuse distal tubular necrosis because among other evidence the renal arteriovenous differences for oxygen and carbon dioxide is normal in patients with anuric renal failure following incompatible blood transfusion (Barker Clark and Crossley 1950)

Studies of the intrarenal blood flow in burned animals have been made by Sevitt (1948) and by Monsaingeon Tanret and Daussy (1949) by the *in vivo* injection of colloidal dyes or suspensions Only multiple small ischaemic foci of irregular distribution were found by Sevitt whilst the majority of glomerular and peritubular capillaries were opened and hyperaemic but many of the animals of Monsaingeon and his colleagues (which were burned more extensively and for longer periods than those of Sevitt) showed either a total renal ischaemia or an ischaemia of the outer two-thirds of the cortex like that described by Trueta and his colleagues Thus the extent and severity of burning influences the renal vascular pattern

Nervous and humoral production of renal vasospasm —Reflex stimulation of the renal nerves could be responsible for the disturbance of the renal and intra renal blood flow because stimulation of the splanchnic nerves produces either total renal ischaemia or the by pass mechanism (Trueta and his colleagues, 1947) The afferent path may be stimulated by baroreceptors in the blood vessels responding to changes in blood volume (Borst, 1948 Cort, 1955) On the other hand a humoral substance may be implicated because Page (1943) found that the plasma of burned dogs developed vasoconstrictor properties for the vessels of the isolated rabbit s ear Intravascular haemolysis may also augment or induce renal vasoconstriction (*vide infra*) The relative values of the nervous and humoral mechanisms is not known but reflex vasospasm from oligaemia is probably more important.

Origin of proximal tubular necrosis —The viable subcapsular rim of cortex in this condition suggests that the tubular damage results from ischaemic anoxia in the distribution of the main artery Taking the clinical histological and experimental evidence together it may be concluded that proximal tubular necrosis results from renal

ligated When the clamping in dogs was for 4–6 hours or longer the animals developed a progressive azotaemia and died within a few days (Van Slyke and his colleagues, 1944, Hamilton, Phillips and Hiller, 1948) Clamping for 3–4½ hours was followed by complete renal or a gross cortical necrosis (de Wardener, 1955) Lesser periods of clamping often produced reversible azotaemia and functional damage Release of the artery 20 minutes to 2 hours after clamping was followed by an immediate resumption of the renal blood flow, but there was evidence of functional tubular damage which was greater the more prolonged the clamping (Phillips and Hamilton, 1948) The rabbit kidney may be more susceptible to ischaemia Arterial clamping for 2 hours was followed by irreversible azotaemia, death within a few days and cortical tubular necrosis (Scarff and Keele, 1943, Badenoch and Darmady, 1947) Burwell (1955), who studied serial histological sections, found that the damage after clamping for 1½–4 hours mainly affected the descending medullary portion of the proximal tubule Badenoch and Darmady (1947) found that lesser periods of clamping (or partial clamping) produced a lower death rate and often a reversible azotaemia They claimed that the histological changes in such animals are comparable to those seen in human "traumatic uraemia" (diffuse distal tubular necrosis) but in view of Burwell's work it is likely that the descending part of the proximal tubule was affected and not the wide ascending limb of Henle

Unfortunately details of urine flow have not been reported in these experiments, but the urea clearance tests carried out by Hamilton, Phillips and Hiller (1948) indicate that secretion of urine did continue when the artery was released 2–3 hours after clamping It is possible that uraemia was accompanied by little or no oliguria in some of the animals and by severe oliguria in others

The period of ischaemia necessary to produce tubular damage in man is not known but the human kidney is not necessarily more resistant to ischaemia than the dog's Brun (1954) thought that 4–6 hours of renal vasoconstriction was necessary before ischaemic anuria occurred

Renal arterial by-pass—Trueta and his colleagues (1947) demonstrated an intrarenal vascular by-pass mechanism The blood for the distal two-thirds or three-quarters of the cortex is diverted through the juxta-medullary glomeruli, the efferent vessels of which loop downwards and drain directly into the tributaries of the renal vein The by-pass is brought about by vasospasm of the interlobular arteries and afferent arterioles which produces an ischaemia of the

Vasoconstriction—Barac (1952) found that injection of heated or lysed red cells into dogs rapidly produced *oliguria but this did not* occur when crystalline haemoglobin or the stroma of red cells was injected It may be that something is liberated during haemolysis which has a vasoconstrictive action on the renal arteries and that this supplements the other mechanisms producing renal ischaemia Indeed Mason and Mann (1931) claimed that vasoconstriction occurred after injection of haemoglobin Haemoglobinaemia enhances the danger of renal failure from renal ischaemia because the injection of haemoglobin caused fatal uraemia in animals subjected to partial renal ischaemia by incomplete clamping of the renal artery (Yuile, Gold and Hinds, 1945)

Oligaemia—It must also be borne in mind that severe haemoglobinuria denotes severe haemolysis and an acute loss of the circulating red cell mass This will not only add to the oligaemia due to loss of plasma but will cause a relatively low haematocrit or haemoglobin value The volume of lost plasma may then be underestimated, the patient may be undertransfused and an undiagnosed oligaemia may persist until haemodilution occurs

Diffuse and focal distal tubular necrosis—The combination of renal ischaemia (from oligaemia and humoral factors) together with the deposition of many casts from frank haemoglobinuria appears necessary for most cases of diffuse distal tubular necrosis

There is evidence that *focal* distal tubular necrosis is produced by considerable haemoglobinuria with little or no oligaemia and possibly by moderate or short lived oligaemia with little or no haemoglobinuria Several extensively burned children with heavy and prolonged haemoglobinuria (who might have been expected to develop renal failure) were *maintained free of oligaemia for the first* few days after burning by transfusion of blood and plasma controlled by repeated blood volume determinations as well as examinations of the peripheral blood (Sevitt 1956a 1956b and subsequent observations) The children died later of causes unrelated to renal failure during life their urine flow and renal function was normal and azotaemia did not develop In most of them only a focal distal tubular necrosis was found in one child who died within a few days of burning, the kidneys contained numerous pigmented casts but showed only focal tubular necroses Had she survived longer the casts may well have been progressively removed by the unobstructed urinary flow and the histological appearance would have come to resemble that observed in other cases of focal distal tubular necrosis

The absence of severe haemoglobinuria in most children with focal

cortical ischaemia of vasomotor origin, that nephrosclerosis often facilitates the renal cortical by-pass and that haemoglobinuria may be a factor in augmenting vasospasm

Haemoglobinuria —Among the many nephrotoxic substances suggested as explanations of acute renal failure are haem compounds They have particular relevance to renal failure after burning because of the frequency and severity of intravascular haemolysis (Chapter 15) Haemoglobinuria results when the plasma haemoglobin rises above the threshold value of about 130 milligrams per 100 millilitres The degree of haemoglobinuria varies considerably, it may be slight and easily overlooked clinically or the urine may be deep red or reddish-brown, it may be transient or last 1 or 2 days

Severe haemoglobinaemia and haemoglobinuria were associated with impairment of renal function in burned subjects and animals by Shen, Ham and Fleming (1943), Goodpastor and his colleagues (1946), Olson and Necheles (1947) and Sevitt (1956a, 1956b) Sevitt found that about 80 per cent of patients with diffuse distal tubular necrosis had had severe haemoglobinuria when the associated renal failure was either oliguric or non-oliguric Haemoglobinuria also occurred in about half of those with proximal tubular necrosis On the other hand, haemoglobinuria occurred in only about 12 per cent of fatally burned patients without tubular necrosis and in about one-third of those with focal distal tubular necrosis Thus the presence of free haemoglobin in the urine is associated with most cases of acute renal failure particularly those who develop diffuse distal tubular necrosis

Blocking of tubules —The manner by which haemoglobinuria induces or predisposes to diffuse distal tubular necrosis is not known with certainty but the histological appearance of many haemoglobin casts which block parts of many distal tubules, help render them focally necrotic and induce tubular rupture, cannot be disregarded as a pathogenetic factor The haemoglobin is already in high concentration in the glomerular filtrate and is readily precipitated in the distal tubules because of the considerable reabsorption of water Epithelial necrosis and tubular rupture may be facilitated in the sites blocked by casts when tubulo-epithelial hypoxia from renal ischaemia is also present In the absence of ischaemic damage the casts may be progressively removed by the continued tubular flow and little or no renal dysfunction or tubular damage would result (*vide infra*) Oliver, MacDowell and Tracey (1951) and Oliver (1953) who advocate the theory of "stopped pipes" have shown by the microdissection technique that local tubular blockage or rupture can interfere with the function of the whole nephron

haemoglobin However the kidney may be unable to excrete sulphate or mannitol particularly if severe oliguria persists and these foreign substances would then accumulate in the body Any possible advantages of solute diuresis could be retained without the disadvantages of sulphate or mannitol by administering a litre or more of 20 per cent glucose intravenously since glucose is metabolized to carbon dioxide and water The diuretic effect of the large doses of ascorbic acid administered to burned dogs by Barac (1953) may have been due to osmotic diuresis

Therapeutic.—When irreversible oliguria and renal failure develop during the shock phase the clinician is faced with a paradox Intravenous plasma continues to be necessary in order to prevent death from circulatory failure, but the giving of large volumes of fluid may be fraught with later danger During the next few days the burn oedema will be reabsorbed but cannot be excreted the circulation may be overloaded and death may occur from pulmonary oedema This danger is lessened by external loss of water from weeping burns and by insensible losses Recommendations are difficult but obviously the patient must not be allowed to die from oligaemia during the shock phase The desirability of later venesection to correct circulatory overloading should be carefully considered and if it is necessary half a volume of packed red cells might be transfused for every volume of blood withdrawn

After the shock phase fluid therapy should just be adequate to replace surface, urinary gastric and respiratory losses but the daily volumes required are more difficult to estimate than in unburned patients with renal failure because of the difficulty in estimating the fluid lost from the burned skin Electrolyte therapy should be controlled as far as possible by repeated estimations of the serum sodium chloride, potassium calcium and bicarbonate values Added calcium will be required potassium salts and fruit juices should be prohibited because of the danger of hyperpotassaemia and acidaemia should be corrected but not at the risk of producing alkalaemia.

There is much less danger of pulmonary oedema in the non oliguric form of renal failure This kind of uraemia might be easily overlooked because severely burned patients who survive the shock phase without developing uraemia are frequently ill Vomiting, tachycardia, pyrexia and a disturbed mental state are not uncommon and as a consequence symptoms of incipient uraemia may be over looked For this reason blood urea estimation should be performed as a routine every 2 or 3 days for the first 7–10 days in all extensively burned patients

distal tubular necrosis suggests that oligaemia alone may have been responsible but that it was insufficient to produce prolonged renal ischaemia, this hypothesis requires further investigation

CLINICAL IMPLICATIONS

Prophylactic.—The importance of adequately combating oligaemia has been stressed Plasma transfusion is important not only in preventing circulatory failure but also as a prophylactic against renal failure Vigilance is particularly necessary when there is haemoglobinuria because the combination of oligaemia and frank haemoglobinuria commonly produces diffuse distal tubular necrosis It cannot be overstressed that in extensively burned patients no delay is warranted in the setting up of an intravenous plasma transfusion the rate and volume of which must meet not only the estimated loss of fluid prior to transfusion but also the current loss In addition to the serial haematocrit or haemoglobin estimations required and the whole blood transfusions recommended (Chapter 15) an indwelling catheter should be passed and a continuous record of the urine flow made Reversible oliguria from inadequate rate of transfusion must be distinguished from the oliguria of renal failure During the first 24 hours or so the urinary output in an adequately transfused adult should normally exceed about 30 millilitres per hour but may not be much in excess of this because of the obligatory retention of water during the "shock phase" (Chapter 13) Nevertheless the maintenance of a relatively normal urine output does not necessarily mean that renal failure is not present

Water-tolerance test —A water-tolerance test may be valuable in distinguishing reversible from irreversible oliguria (Cope and Moore, 1947) Several hundred millilitres of 5 per cent glucose or normal saline (not plasma) are rapidly transfused and the response of the urine flow is noted Reversible oliguria from inadequate transfusion will be indicated by a prompt increase in the rate of urinary secretion

Osmotic diuresis —Measures directed to maintain a dilute tubular urine have been proposed in preventing acute renal failure Intravenous isotonic sodium sulphate was favoured by Olson and Necheles (1947) because it was very effective in producing diuresis in burned dogs when given during the first hour or two The infusion of 15 per cent mannitol was proposed by Dudley, Batchelor and Sutherland (1957) in patients with haemoglobinuria because they thought that the osmotic diuresis produced would dilute and increase the urine flow through the distal tubules and prevent the precipitation of

Trueta, J., Barclay A E., Daniel, P., Franklin, K. J., and Pritchard M M L. (1947) *Studies of the Renal Circulation* Oxford Blackwell
Van Slyke, D D., Phillips, R. A., Hamilton, P B Archibald, R. M Dole, V P., and Emerson, K (1944) *Trans Ass Amer Phys* **58**, 119
Vogt, W (1929) *Virchows Arch* **237** 140
de Wardener H E. (1955) *Lancet* I 580
Wertheim, (1867). *Wien. med Presse* **8**, 1237 (Quoted by Pack, 1926.)
Yuile, C. L., Gold M A., and Hinds, E. G (1945) *J exp Med* **82**, 361
Zinck K. H (1940) *Klin Wschr* **19** 78

The prognosis of burned patients with renal failure is grave but the patient's chance of survival may have increased with recent advances in therapy such as high-calorie low-nitrogen feeding, ion exchange resins and blood dialysis (artificial kidney)

REFERENCES

Badenoch, A W, and Darmady, E M (1947) *J Path Bact*, **59,** 79

Barac, G (1952) In *Proc Sixth Internat Cong Compar Path*, 357

— (1953) *Arch internat Physiol*, *Liege*, **61,** 407, 411

Barker, H G, Clark, J K, and Crossley, A P (1950) *Surg Forum*, 496

Borst, J G G (1948) *Acta med Scand*, Suppl, 207

Brown, C E, and Crane, G L (1943) *J Amer med Ass*, **122,** 871

Brun, C (1954) *Acute Anuria* Copenhagen

Bull, G M, Joekes, A M, and Lowe, K G (1950) *Clin Sci*, **9,** 379

— and Dible, J H (1953) In *Recent Advances in Pathology*, 6th Ed, p 284 (Ed by G Hadfield) London, Churchill

Burwell, R G (1955) *J Path Bact*, **70,** 387

Bywaters, E G L, and Beall, D (1941) *Brit med J*, **1,** 427

— and Dible, J H (1942) *J Path Bact*, **54,** 111

Christophe, L (1939) *La mort des brûlés*, Paris

Cope, O, and Moore, F D (1947) *Ann Surg*, **126,** 1010

Cort, J H (1955) *Physiol Bohemoslovenica*, **4,** 14

Dudley, H A F, Batchelor, A D R, and Sutherland, A B (1957) *Brit J plast Surg*, **9,** 275

Dunn, J S, Gillespie, M, and Niven, J S F (1941) *Lancet*, **2,** 549

Dziemian, A J (1948) *Fed Proc*, **7,** 29

Erb, I H, Morgan, E M, and Farmer, A W (1943) *Ann Surg*, **117,** 234

Gibson, T (1945) In *Studies of Burns and Scalds* M R C Special Report Series No 249

Goodpastor, W E, Levenson, S M, Tagnon, H J, Lund, C C, and Taylor, F H L (1946) *Surg Gynec Obstet*, **82,** 652

Graber, I G, and Sevitt, S (1957) In the Press

Hamilton, P B, Phillips, R A, and Hiller, A (1948) *Amer J Physiol*, **152,** 517

Haynes, B W, DeBakey, M, and Denman, F R (1951) *Ann Surg*, **134,** 617

Keele, C A, and Slome, D (1945) *Brit J exp Path*, **26,** 151

Lucké, B (1946) *Mil Surg*, **99,** 371

Luetscher, J A, and Blackfan, S S (1943) *Ann intern Med*, **18,** 756

Lauson, H D, Bradley, S E, and Cournand, A (1944) *J clin Invest*, **23,** 381

Martineau, P C, and Hartman, F W (1947) *J Amer med Ass*, **134,** 429

Mason, J B, and Mann, F G (1931) *Amer J Physiol*, **98,** 181

Monsaingeon, A, Tanret, P, and Daussy, M (1949) *Pr Med*, **81,** 1221

Oliver, J (1953) *Amer J Med*, **15,** 535

— MacDowell, M, and Tracey, A (1951) *J clin Invest*, **30,** 1305

Olson, W H, and Necheles, H (1947) *Surg Gynec Obstet*, **84,** 283

Pack, G T (1926) *Arch Path Lab Med*, **1,** 767

Page, I H (1943) *Amer J Physiol*, **139,** 386

Phillips, R A, and Hamilton, P B (1948) *Amer J Physiol*, **152,** 523

Scarff, R W, and Keele, C A (1943) *Brit J exp Path*, **24,** 147

Sevitt, S (1948 and 1957) Unpublished observations

— (1956a) *J clin Path*, **9,** 12

— (1956b) *Ibid*, **9,** 222

Shen, S C, Ham, T H, and Fleming, E M (1943) *New Engl J Med*, **229,** 701

Smith, H W (1951) *The Kidney*, p 778 Oxford Oxford Medical Publications

Teschan, P E, Post, R S, Smith, L H, Abernethy, R S, Davis, J H, Gray, D M, Howard, J M, Johnson, K E, Klopp, E, Mundy, R L, O'Meara, M P, and Rush, B F (1955) *Amer J Med*, **18,** 172

Trueta J Barclay A. E. Daniel P Franklin K. J., and Pritchard, M M L. (1947). *Studies of the Renal Circulation* Oxford Blackwell.
Van Slyke, D D., Phillips, R. A., Hamilton, P B Archibald, R. M., Dole V P., and Emerson, K. (1944) *Trans Ass Amer Phys.*, 58, 119
Vogt, W (1929) *Virchows Arch.* 237 140.
de Wardener H. E. (1955) *Lancet* 1 580
Wertheim, (1867) *Wien med Presse* 8, 1237 (Quoted by Pack 1926.)
Yulle, C. L., Gold, M A., and Hinds, E. G (1945) *J exp Med* 82, 361
Zinck K. H (1940) *Klin Wschr.*, 19 78

CHAPTER 15

THE ANAEMIA OF BURNS

SOME degree of anaemia is found in most patients with burns of more than 10 per cent of the body area, and those with extensive whole skin-loss burns rapidly develop a moderately severe anaemia which resists all known forms of therapy The haemoglobin level always falls when there is more than 5 per cent whole skin-loss and the anaemia is generally normocytic and normochromic Even without operative loss the blood haemoglobin and red cell levels may fall to about 8 grammes per 100 millilitres and 2–3 million per cubic millimetre or less, and repeated blood transfusions are required to maintain a relatively normal peripheral blood picture and red cell volume When the burn is healed the anaemia disappears but this does not usually occur until less than 2 per cent of the body area remains unhealed

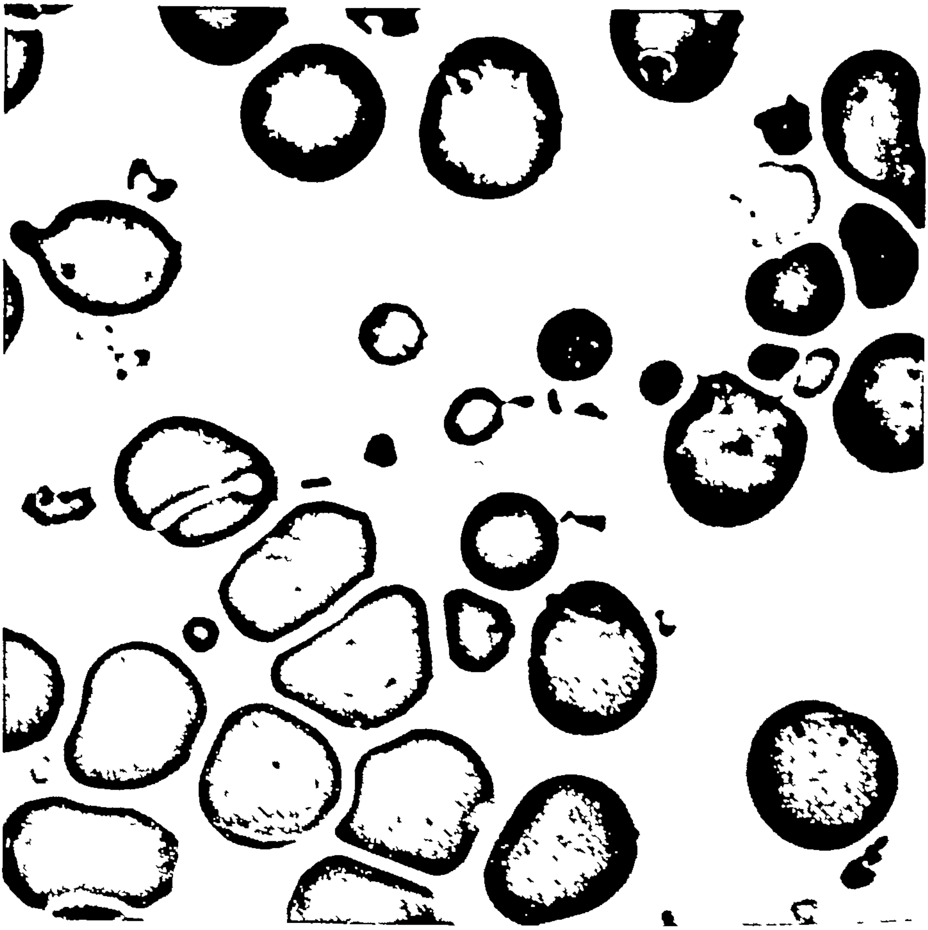
Blood volume estimations on patients with large whole skin-loss burns requiring excision and grafting have shown that the total loss of blood from burning to discharge from hospital may amount to more than the entire blood volume In most patients the greatest blood loss is from haemorrhage during excision of the burn, and during the operation blood transfusion equivalent to the loss is required In their study of red cell loss in 150 patients with large burns, Topley and Jackson (1957) found that the average loss of blood during grafting operations amounted to 135 per cent of the patient's red cell volume Their blood volume studies also showed a considerable loss of red cells during the first 2–3 weeks after burning, that is prior to the first grafting operation During this period the red cells lost averaged 45 per cent of the red cell mass and most of the cells disappeared during the first 48 hours

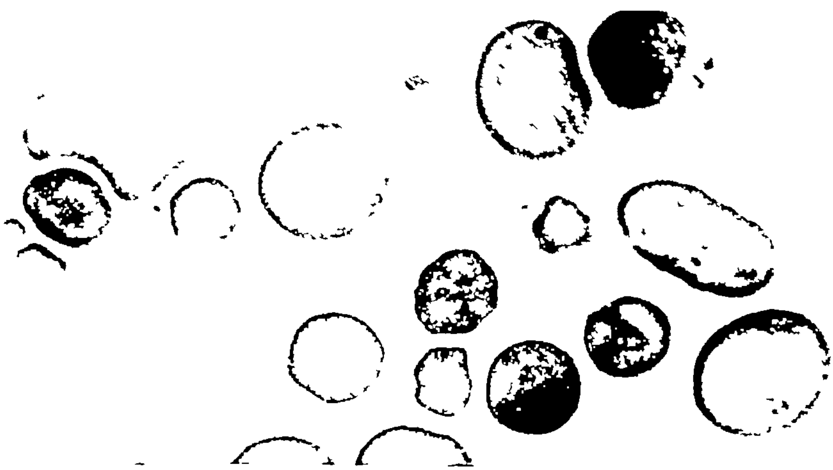
The factors involved in the true post-burn anaemia are complex and not fully understood They include (1) a direct heat effect on erythrocytes circulating through the skin at the time of burning, (2) a disappearance of red cells distinct from the heat effect and partly due to trapping by capillary stasis (3) a disturbance of haemoglobin synthesis possibly related to a nutritional-metabolic disturbance, and (4) infection of the burned skin

DIRECT HEAT EFFECT

Heating of blood up to 50 C alters the permeability of the red cells and allows potassium to escape, but morphological changes are not detectable (McLean Moritz and Roos 1947) Heating above 50 C produces permanent morphological changes the nature of which depends on the temperature and duration of heating The alterations are the direct effect of heat and not the result of changes in the plasma. In addition to altered morphology the red cells become osmotically and mechanically more fragile and lyse (Schultze, 1865 Silbermann 1890 Isaacs Brock and Minōt, 1924–1925 Shen Ham and Fleming, 1943 Brown 1945 1946 Ham and his colleagues 1948) Similar changes are found in the blood of extensively burned animals Haemoglobinaemia and haemoglobinuria are observed when heated blood is transfused into normal animals (von Lesser 1880 Pfeiffer 1905) and the transfused cells disappear from the circulation within a few hours (Ham and his colleagues, 1948)

Similar erythrocyte changes occur in extensively burned patients, presumably because the blood circulating in the skin at the time of burning is affected by the heat The extent to which the patient s blood is altered depends on the temperature extent and duration of burning but even in patients with deep extensive burns only a moderate proportion of the cells are affected The microscopic changes are most evident soon after burning There is a prompt microspherocytosis, which may affect up to 5 per cent of the erythrocytes with the budding and fragmentation of cells and the formation of microcytes (1–3 microns in diameter) and crenated forms (Figs 55 and 56) Most of the abnormal forms disappear within 12–24 hours but some microspherocytes and occasional microcytes can be found in blood films during the next few days The percentage of microcytes in early blood smears can be used as a rough guide to the total amount of blood likely to be destroyed during the first 2 days (Topley 1956) The spherocytosis coincides with an increase in the osmotic and mechanical fragilities of the cells but the mean cell volume is not significantly increased The increased fragility affects up to about 10 per cent of the red cells which may lyse in normal saline or plasma Whole blood removed from many recently and extensively burned patients undergoes a progressive but limited haemolysis within a few hours of collection and the plasma haemoglobin content rises considerably The saline fragility curves indicate that most of the red cells are normal but that they are mixed with a proportion of excessively fragile cells The increased fragility usually lasts 12–24 hours, after which the osmotic fragility as normally tested returns to normal or to a little below normal After this





FIGS 55 and 56 —Microcytes red cell fragments and spherocytes in blood films from two extensively burned patients made a few hours after injury Note the budding of one cell in top figure Microcytes do not spread well and should be searched for in the head of the film (Leishman stain)

period special tests suggest that excessive fragility of some cells persists and this may be a latent heat effect

One other feature is worthy of note Occasionally difficulty is encountered in the Rhesus typing of the blood of recently and extensively burned patients and false Rh negative (D-negative) results may be obtained during the first day or two after burning in patients whose blood is subsequently found to be D positive The phenomenon is infrequent but occurs when efficient anti D antisera are used for typing and appears to be a heat effect on red cells It is probably related to the heat lability of the D antigen found *in vitro* by Ponder and Ponder (1952)

Haemoglobinuria and haemoglobinaemia.—Haemoglobinuria follows haemoglobinaemia from intravascular haemolysis when the plasma haemoglobin exceeds the renal threshold level of 130–140 milli grams per 100 millilitres The initial haemolysis commences soon after burning. The serum may be red and contain 50–300 milligrams per 100 millilitres of haemoglobin or more during maximum haemoly sis In severely burned dogs Olson and Necheles (1947) found 500–3 000 milligrams of haemoglobin per 100 millilitres in the plasma but such values are exceptional Spectroscopy and Schumm s test often reveal methaemalbumin as well as free oxyhaemoglobin

Haemoglobinuria has been long known in burned patients and is not infrequent when the area burned exceeds 30 per cent of the body surface Shen Ham and Fleming (1943) found gross haemoglobinuria in 9 out of 12 patients with 45–65 per cent burns and this frequency accords with the author s experience (Sevitt 1956) The relationship of haemoglobinuria to renal failure is discussed in Chapter 14 The degree of haemoglobinuria varies but the urine may be dark red brown or black in colour and the maximum haemoglobin content can amount to 0 5 gramme, or even 1 gramme per 100 millilitres of urine The urine is usually acid in reaction The pigment is a mixture of oxyhaemoglobin and methaemoglobin but myohaemoglobin is absent unless there is destruction of muscle from associated injuries or electric burns Part of the haemoglobin is in solution and part is a granular precipitate which contains many haemoglobin casts and a little haemosiderin Slight degrees of haemoglobinuria are more frequent but are often not diagnosed in such cases the benzidine test of the boiled urine is positive and spectroscopy may reveal the characteristic absorption bands

It is not generally known that haemoglobinuria is often biphasic or intermittent Often the urine is dark red an hour or so after burn ing and the initial intense haemoglobinuria continues for hours

Gradually the urine clears and its colour returns to normal, but hours later deep coloration by blood pigment reappears (Fig 57) Sometimes the initial haemoglobinuria is absent and the urine first becomes affected 12–24 hours after burning—the delayed effect In some patients a continuous episode of severe haemoglobinuria persists for 24–48 hours which may be interpreted as the merging of the initial and delayed effects The initial haemoglobinuria results from the effects of heat on red cells circulating in the skin at the time of burning and the delayed episode may also be due to this The rapid haemoglobinuria represents the intravascular destruction of the most badly damaged cells and the later episode is presumably the result of the later destruction of cells which suffered less severe immediate

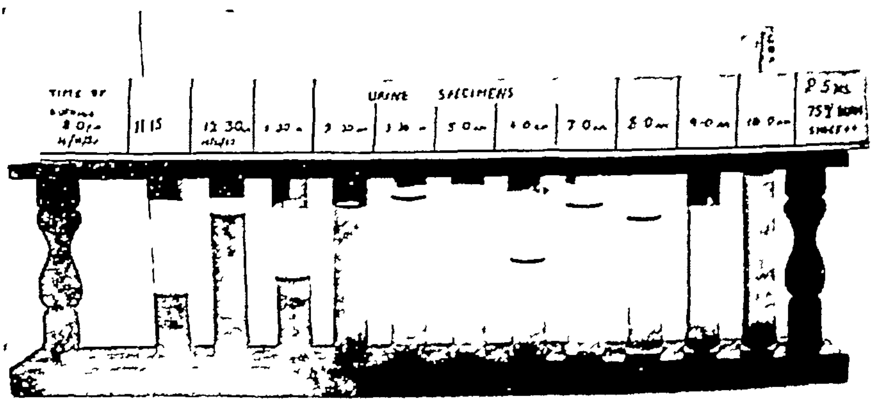


FIG 57 —Intermittent haemoglobinuria after burning The urine at first is dark with haemoglobin, then it clears but later it becomes dark again

damage Both account for or contribute to the progressive lowering of the red cell volume found within 2 or 3 days of burning (*vide infra*)

Early loss of red cell volume —The initial heat effect on the red cells is associated with a fall in the total red cell volume during the first 6–12 hours after burning This was first demonstrated by Schievers (1936) who determined the red cell volume of burned rabbits by the carbon monoxide technique It has since been confirmed in burned animals and in patients after a transfusion of red cells appropriately labelled antigenically or with radioactive phosphorus or chromium (Salzberg and Evans, 1950 Raker and Rovit, 1954, Topley, 1954, Davies and Topley, 1956) The results are in agreement with those from the saline fragility tests and show an average fall in the red cell volume of 8–12 per cent during the first 6–12 hours after burning

Thus the early loss of cells from a direct heat effect is acute but limited

Splenic contraction.—In burned dogs an acute but short lived phase of increased blood and red cell volume may occur before oligaemia sets in (Keeley Gibson and Pijoan 1939 Mukhin 1947) This is apparently the result of a sharp splenic contraction which adds a significant mass of red cells to the circulation Mukhin (1947) demonstrated this contraction in dogs whose spleens had been brought under the abdominal skin at a prior laparotomy and Keeley Gibson and Pijoan (1939) found that the initial rise in the red cell volume after burning was abolished in dogs subjected to previous splenectomy In man the importance of splenic contraction is not known but is likely to be very variable and the initial rise in the red cell volume has not yet been demonstrated

FURTHER LOSS OF RED CELL VOLUME

Most of the red cells which are lost disappear between 12 and 48 hours after burning the loss merges with that which occurred earlier but is usually considerably greater In the experience of Davies and Topley (1956) with extensively burned patients the average loss was about 30 per cent of the normal red cell volume and in several patients was as much as 60 per cent during this period This gross loss of erythrocytes cannot all result from a heat effect on the cells because *transfused* blood disappears as rapidly as the patient s own cells

The acute loss during the first 48 hours the shock period, is im portant to recognize for two reasons The degree of plasma oligaemia is masked by the red cell loss when only the peripheral blood (haemoglobin or haematocrit) is examined and for the same reason the anaemia itself is masked This means that plasma transfusion may be inadequate during the shock period and an undiagnosed oligaemia with its attendant risks of circulatory and renal failure will continue until haemodilution occurs During the next few days the peripheral haemoglobin value will progressively fall as the plasma volume returns to normal and only by the fifth or sixth day after burning will the peripheral blood haemoglobin level reflect the earlier loss of red cells (Fig 45) In another example, an apparently normal haematocrit value of 45 per cent on the first day disguised considerable red cell and plasma oligaemia, but the extent of red cell loss was revealed when the haematocrit value progressively fell to 30 per cent by the sixth day after burning

The cause of this continuing red cell loss is more complex than the earlier loss and requires further investigation The probable causes are (1) continuation of haemolysis and extravascular destruction of

red cells from the heat effect on the cells and possibly from other causes, (2) capillary stasis in the burned skin, and (3) internal loss from congestion and haemorrhage into the intestinal tract and congestion of other viscera

Haemolytic jaundice and anaemia.—Occasionally an extensively burned patient rapidly develops an acute haemolytic jaundice Intravascular haemolysis and haemoglobinuria after burning are considerable and prolonged, there is a rapid and considerable increase in the serum bilirubin (5–10 milligrams per 100 millilitres or more), the direct Van den Bergh reaction is negative, in children the peripheral blood may contain numbers of normoblasts, and the patient becomes jaundiced but there is no bilirubin in the urine There may be an initial difficulty in blood grouping and cross-matching for transfusion due to excessive rouleaux formation or auto-agglutination of the patient's cells and pan-agglutinability of his serum, but this difficulty is usually temporary and disappears within a day or two Fixation of globulin on the patient's red cells cannot be detected by the direct Coombs's test using a rabbit serum prepared by the injection of normal human globulin

In other patients the haemolytic process is less severe and the evidence of destruction of cells is based on a falling haemoglobin and red cell count, an increased serum bilirubin level (up to 1 or 2 milligrams per 100 millilitres), an increased excretion of urobilin and other degradation products in the urine and faeces (Anderson and Semeonoff, 1945, Moore and his colleagues, 1946, James, Purnell and Evans, 1951) and an excessive rate of disappearance of red cells both transfused and those of the patient (Davies and Topley, 1956) In patients who die during this period histological examination reveals haemosiderin in the Kupffer cells of the liver (Fig 81) and in the spleen, a reticulo-endothelial hyperplasia and sometimes erythrophagocytosis in the bone marrow and spleen

The haemolysis is at least partly the result of the direct effect of heat on erythrocytes but there may also be other causes There may be a disturbance of the lipoid envelope of the erythrocyte or a fixation on the cell surface of some abnormal protein or enzyme or other substance possibly picked up by erythrocytes as they circulate through the burned skin

Red cell loss into the skin and viscera —*Destruction of red cells* cannot account for all the loss since the amount of urobilin excreted in the urine and faeces is less than would be expected Loss of red cells into the burned skin probably contributes considerably to the loss of

red cell volume found during the first 2 or 3 days The inflammatory reaction in the burn commonly results in a stagnant and finally static dermal capillary blood flow which may also involve the subcutaneous capillaries (Chapter 3) The erythrocytes in these numerous distended channels are permanently lost and cannot return to the circulation The iron content of the burned skin of pigs was determined by Moritz (1947) who found it greatly increased (5–10 times normal) in very hyperaemic burns He calculated that as much as 30 per cent of the erythrocytes of an extensively burned animal could be accounted for in its skin and suggested that a large proportion of the circulating blood may be pooled in the skin and subcutaneous tissues as a result of burning Further investigations are required to determine how much of the blood in burned skin can return to the circulation and how much is permanently lost The amount per unit area probably varies with the severity of burning.

Other sources of red cell trapping or loss are congestion of the internal viscera, the not infrequent mucosal haemorrhage of the intestinal tract (Figs 77 and 78) and melaena Some of the loss in the skin and viscera must be temporary serial blood volume studies have sometimes shown a rise in the total red cell volume a few days after burning even though transfused cells are disappearing a finding which suggests that trapped cells have returned to the circulation The phenomenon is best seen in patients with burns involving 15–20 per cent of the body area (Topley 1956) whilst in those more extensively burned the return of trapped cells may be obscured by losses from other causes On the other hand the loss by trapping and stasis may be more extensive and permanent Brooks and his colleagues (1950) suggested that the changes which follow sludging of the blood in burned subjects such as extravascular diapedesis and haemorrhage and minute intravascular thrombi may contribute to the anaemia

LATER CAUSES OF ANAEMIA

Continuing red cell loss.—Disappearance of red cells may continue for weeks but the degree and rate of loss is much less than during the first 2 or 3 days Usually both the patient s and previously transfused cells disappear from the circulation at the same rate and at about the normal 1 per cent per day (Davies and Topley 1956) The loss is variable and is often obscured by other causes of anaemia such as bleeding during operative excision of the burns Part of the loss must result from the slight continuous oozing of red cells from the burned or granulating skin, but part may result from extravascular destruction

Haemoglobin synthesis—There is some evidence that an impaired rate of red cell formation contributes to the anaemia and that the metabolism of iron, porphyrin and globin is disturbed Moore and his colleagues (1946) found that the uptake of radioactive iron (^{59}Fe) by newly formed erythrocytes was often much lower than normal, and when burned dogs and one burned patient were fed with glycine labelled with heavy nitrogen (^{15}N) there was a marked depression of the uptake of radioactivity by the newly formed cells (James and his colleagues, 1954) However Davies and Topley (1956) point out that these results might be explained by a relatively greater increase in the use of iron or glycine for other purposes such as cellular multiplication Other evidence also suggests a disorder of haemoglobin metabolism the free red cell protoporphyrin is increased, protoporphyrinuria occurs, there is probably some alteration in the alkaline denaturation, and possibly some reduction in the electrophoretic mobility and oxygen capacity of the haemoglobin (Baar, 1956)

Protein loss and haemoglobin synthesis—Braithwaite and Moore (1948) thought that a disturbance of nutrition was involved in the anaemia of burns They claimed that the lowered haemoglobin level of the blood was related to hypoproteinaemia and the negative nitrogen balance, and that as the daily excretion of urinary urea rose the blood haemoglobin and plasma protein levels fell They concluded that the operative factor was the drainage of protein from the body which they suggest interfered with haemoglobin synthesis On the other hand Brown (1945) could find no relationship between the degree of anaemia and the plasma-protein level, so that whilst depletion of body protein may contribute it is not essential for the development of the anaemia

Haemopoiesis—Reticulocyte counts have been studied by Brown (1945), Moore and his colleagues (1946), Demidova, Maslennikova and Kachanova (1949), Davies and Topley (1956) and by the author In patients with little or no anaemia there is no increase in the count, but in anaemic patients a rise in the proportion of reticulocytes occurs during the second to the fourth weeks after burning The maximum level varies but in most patients it is no greater than 3 per cent of the red cells, but an earlier and greater reticulocytosis (5–10 per cent) occurs in patients with a rapidly developing anaemia Davies and Topley (1956) stated that the reticulocyte rise was related to the degree of anaemia before blood transfusion was started and to the rate of disappearance of red cells but not to the extent of burning above a minimum amount The presence of macrocytes and

polychromatic cells in the peripheral blood also indicates an increase in the degree of haemopoiesis

Bone marrow studies do not appear to have been reported and in the author's experience a moderate hyperplasia, some degree of macronormoblastosis and reticuloendothelial hyperplasia occur There is no evidence of an absolute depression of marrow function but the hyperplasia seems to be insufficient to balance the fall in the red cell count

Infection —Anaemia is particularly frequent and severe in patients with extensive whole skin loss burns, and is less common and less severe when the burns are superficial in character and heal within 2 or 3 weeks It is well known that whole skin loss burns commonly become contaminated with a variety of micro-organisms (Chapter 6) and it has been suggested that the continuing anaemia of burns is related to the infection of the burned skin rather than to the burn itself (Cope 1947) After the first week there is a significant relationship between the degree of red cell loss and the area of full thickness skin loss (Davies and Topley 1956) The anaemia of burns disappears when the wound is healed by grafting or otherwise and this may be due to the disappearance of the local infection when the burn is closed There are haematological similarities between the anaemia of infection and that of burns In both there is a disturbance of haemoglobin synthesis and an unexplained disappearance of red cells

The connexion between burn anaemia and infection is difficult to prove or to disprove, and only an analysis of infected and uninfected patients with otherwise comparable burns would be conclusive Such a comparison is probably impossible to achieve and indeed the anaemia might be related to certain bacteria rather than infection *per se* Jackson Lowbury and Topley (1951) found that contamination of the burned skin with *Ps pyocyanea* was associated with an increase in the incidence of anaemia In their controlled clinical prophylactic trial of locally applied polymyxin E (to which *Ps pyocyanea* is sensitive) they found that 4 out of 25 patients (16 per cent) receiving polymyxin developed a haemoglobin level of less than 80 per cent of the average normal whilst 11 out of 33 (33 per cent) of the control patients not receiving polymyxin developed such an anaemia

Infection may produce anaemia by increasing the amount of haemorrhage from the sloughing or granulating burned surface as well as by systemic effects The local loss of red cells is often not apparent because of the local breakdown of haemoglobin pigment

into colourless substances In exceptional patients the local haemorrhage is obvious and persistent and is an important source of the anaemia For example 3 cases of chronically infected burns with persistent local oozing were described by Altemeier and Carter (1942) Continuous capillary bleeding from the granulating surfaces produced a serious anaemia and hypoproteinaemia and did not cease until the burns were treated with applications of zinc peroxide

CLINICAL APPLICATIONS

From their extensive experience of the anaemia in burned patients Topley and Jackson (1957) found that repeated estimations of the red cell volume were valuable during the first few days, particularly when treating the acute red cell loss in patients with large burns and maintaining their blood volume during the shock period Recognizing that facilities for red cell volume estimations are not generally available, they point out that early *massive* red cell loss occurs most often in the most extensively burned patients, particularly when there is much full-thickness skin destruction In such patients gross haemoglobinuria and the presence of microcytes and fragmented cells in early blood films are particularly common and indicate a considerable red cell loss In them it is particularly important to prevent the oligaemia, which may go undiagnosed because of the normal or only slightly elevated peripheral haemoglobin or haematocrit value They offer the following guide to clinicians

Patients with burns on less than 10 *per cent of the body area* —Blood transfusion is not routinely required

Patients with burns 10–20 *per cent of the body area* (*usually* 2–10 *per cent full-thickness skin-loss*) —Blood transfusion during the first few days is probably unnecessary but haemoglobin estimates are required every 2 or 3 days to detect anaemia and the patient should be transfused accordingly

Patients with burns 20–40 *per cent of the body area* (*usually* 10–30 *per cent full-thickness skin-loss*) —During the first 12 hours after burning a blood transfusion equivalent to 20 per cent of the patient's blood volume should be given and the haematocrit should be maintained between 10 per cent and 20 per cent above its expected normal (for patient's height and weight) by transfusion of plasma, that is, a red cell loss of up to 10 per cent should be assumed During the following 36 hours a further transfusion equivalent to 20 per cent of the blood volume should be given if it is clinically indicated by oliguria, cyanosis, cold extremities or haemoglobinuria, or if more than 2 per cent

of microcytes are present in the head of a stained blood film made on admission Repeated haemoglobin estimates are necessary later

Patients with burns involving more than 40 *per cent of the body area (usually more than* 30 *per cent whole skin-loss)* —During the first 12 hours transfuse with blood equivalent to 20 per cent of the patient s blood volume and maintain the haematocrit at the normal value with plasma that is assume a 20 per cent loss of red cells During the next 36 hours transfuse a further 20-60 per cent of the blood volume when there are clinical indications Serial blood volume estimates are most valuable in these patients After 48 hours repeated haemoglobin determinations are required

REFERENCES

Anderson A B., and Semeonoff E. (1945) In *Studies of Burns and Scalds* p 166 M R.C Special Report Series No 249
Altemeier, W A. and Carter B N (1942) *Ann Surg* 115, 1118
Baar S (1956). Personal communication
Braithwaite F., and Moore, F T (1948). *Brit J plast Surg*, 1 81
Brooks, F Dragstedt, L. R., Warner L. and Knisely M H. (1950) *Arch Surg* 61 387
Brown A. (1945) In *Studies of Burns and Scalds* p 114 M R.C. Special Report Series No 249
— (1946) *J Path. Bact* 58, 367
Cope O (1947) *Surg Gynec Obstet*., 84 999
Davies, J and Topley, E. (1956) *Clin Sci.* 15, 135
Demidova M. N., Maslennikova, G M., and Kachanova, E V (1949) *Khirurgia* No 4 22
Ham, T H., Shen, S. C. Fleming, E. M. and Castle W B (1948) *Blood* 3, 373
Isaacs, R. Brock, B., and Minot, G R. (1924-25) *J clin. Invest*., 1 425
Jackson D McG., Lowbury E J L., and Topley E. (1951) *Lancet* 2, 137
James, G W Abbott, L D Brooks, J W and Evans, E. I (1954) *J clin. Invest*., 33, 150
— Purnell, O J and Evans, E. I (1951) *Ibid* 30 191
Keeley J L., Gibson, J G., and Pijoan, M (1939) *Surgery* 5 872
von Lesser L. (1880) *Virchows Arch*., 79 248.
McLean, R., Moritz, A. R., and Roos, A. (1947) *J clin Invest*., 26, 497
Moore, F D., Peacock, W C., Blakely E., and Cope, O (1946) *Ann. Surg* 124, 811
Moritz, A R. (1947) *Amer J Path.* 23, 915
Mukhin, I A. (1947) *Khirurgia* No 5 30
Olson, W H and Necheles, H. (1947) *Surg Gynec Obstet*., 84 283
Pfeiffer H (1905) *Virchows Arch* 180 367
Ponder R and Ponder E. (1952) *Nature* 170 928
Raker J W., and Rovit, R. L. (1954) *Surg Gynec Obstet* 98, 169
Salzberg, A M., and Evans, E. I (1950) *Ann Surg*., 132, 746
Schievers, J (1936) *Arch int Pharm. Ther* 52, 452
Schultze M (1865) *Arch micro Anat*., 1 1
Sevitt S (1956) *J clin Path*., 9 12.
Shen, S C Ham, T H., and Fleming, E. M (1943) *New Engl J Med.* 229 701
Silbermann O (1890). *Virchows Arch.* 119 488
Topley E. (1954). *Proc R. Soc Med*., 47 230
— (1956) Personal communication.
— and Jackson, D McG (1957) *J clin. Path.* 10 1

CHAPTER 16

CHANGES IN WHITE CELLS, PLATELETS AND CLOTTING FACTORS

BLOOD LEUCOCYTES

THE early effects of burning are a neutrophil leucocytosis accompanied by eosinopenia and a degree of lymphocytopenia Leucocytosis may reappear and eosinophilia may develop

NEUTROPHIL LEUCOCYTOSIS

The early increase in the total white blood count is well known and has been studied by Locke (1902), McIver (1933), Brown (1945), Demidova, Maslennikova and Kachanova (1949), Sevitt (1951) and others Leucocytosis in burned patients (Fig 58) has been classified into (1) an early or *primary* wave, and (2) a later or *secondary* wave (Sevitt, 1951) and further episodes may occur

The onset of the primary leucocytosis is rapid The total count, which is high within a few hours of burning is often at its peak in 6–12 hours and always within 24 hours, 80–95 per cent of the cells are neutrophil polymorphs The count then falls, often rapidly at first and by the second to the fourth day reaches normal levels Thus the primary wave lasts 1 to 3 days In some patients the early high count subsequently diminishes but still remains above normal for 4–6 days after burning, rising again with the second phase of leucocytosis The peak values of the primary wave roughly depend on the extent of burning Total white cell counts of 10,000–15,000 per cubic millimetre of blood are usual when the burn involves less than 10 per cent of the body surface, but in some of these patients an early leucocytosis does not occur In those with larger burns counts above 20,000 per cubic millimetre are common and values of 40,000 or more may be found in extensively burned, shocked patients Rarely the count reaches 70,000, and such values carry a bad prognosis

The secondary neutrophil wave begins 5–10 days after burning Occasionally it develops even when the primary leucocytosis was absent The white count increases to a maximum and then declines to normal levels usually 3–8 days later The peak values are lower than those of the primary wave and are usually below 13,000 per

cubic millimetre when the burned area is less than 10 per cent of the body surface in some of these patients the secondary wave is absent The maximum counts are usually higher in those more extensively burned and are commonly greater than 15 000 per cubic millimetre

In both primary and secondary waves the polymorphs are predominantly young forms metamyelocytes are not uncommon and myelocytes may appear in the p ripheral blood particularly in children Toxic or rather degenerative granulation is common coarse lilac granules may be abundant and numbers of polymorphs may be swollen and vacuolated Locke (1902) thought that many leucocytes are easily torn and concluded that considerable destruction takes place Polymorphs containing pale blue stained circumscribed areas in the cytoplasm known as Döhle bodies are often found (Weiner and Topley 1955) They appear during the first day or two and are more common and numerous in patients with extensive whole skin loss burns Their significance is unknown but they are probably a degenerative manifestation

Systematic bone marrow studies have not been reported but the author has found a relative increase in the cells of the granular series in a number of sternal marrow smears

Pathogenesis.—The primary leucocytosis is directly related to the burning injury and is analogous to the early leucocytosis which follows other forms of trauma It cannot be related to the early *inflammation* in the burned skin because this is not characterized by a leucocytic migration The fall in the white cell count between the primary and secondary waves may reflect the interval between the early aseptic inflammation of the burn and later infection but Weiner and Topley (1955) suggested that it results from a rapid loss of leucocytes into the burned skin The secondary leucocytosis is likely to be a response to later inflammatory changes in the burned skin and Brown (1945) suggested that infection of the raw burned surfaces was responsible This may be so but an analysis of the bacteriology of burns in a series of patients shed no light on the matter (Sevitt, 1951)

EOSINOPENIA

The first reference to eosinopenia in burned patients was made by Schreiner and Puckso (1925) and it was noted by Demidova and her colleagues (1949) but it was not until the availability of ACTH and cortisone stimulated an enquiry into adrenocortical activity that systematic studies of the blood eosinophils were made (Sevitt 1951 1954 Evans and Butterfield 1951 Wight and her colleagues, 1953) using direct eosinophil counts The changes in the eosinophil count

CHAPTER 16

CHANGES IN WHITE CELLS, PLATELETS AND CLOTTING FACTORS

BLOOD LEUCOCYTES

THE early effects of burning are a neutrophil leucocytosis accompanied by eosinopenia and a degree of lymphocytopenia Leucocytosis may reappear and eosinophilia may develop

NEUTROPHIL LEUCOCYTOSIS

The early increase in the total white blood count is well known and has been studied by Locke (1902), McIver (1933) Brown (1945) Demidova Maslennikova and Kachanova (1949) Sevitt (1951) and others Leucocytosis in burned patients (Fig 58) has been classified into (1) an early or *primary* wave and (2) a later or *secondary* wave (Sevitt 1951) and further episodes may occur

The onset of the primary leucocytosis is rapid The total count, which is high within a few hours of burning is often at its peak in 6–12 hours and always within 24 hours, 80–95 per cent of the cells are neutrophil polymorphs The count then falls, often rapidly at first and by the second to the fourth day reaches normal levels Thus the primary wave lasts 1 to 3 days In some patients the early high count subsequently diminishes but still remains above normal for 4–6 days after burning rising again with the second phase of leucocytosis The peak values of the primary wave roughly depend on the extent of burning Total white cell counts of 10,000–15,000 per cubic millimetre of blood are usual when the burn involves less than 10 per cent of the body surface but in some of these patients an early leucocytosis does not occur In those with larger burns counts above 20,000 per cubic millimetre are common and values of 40,000 or more may be found in extensively burned, shocked patients Rarely the count reaches 70 000 and such values carry a bad prognosis

The secondary neutrophil wave begins 5–10 days after burning Occasionally it develops even when the primary leucocytosis was absent The white count increases to a maximum and then declines to normal levels usually 3–8 days later The peak values are lower than those of the primary wave and are usually below 13,000 per

often heralded by a slight increase in the count but frequently this is abrupt. The eosinophil concentration increases progressively for several days to reach a peak which may vary from 70 to 500 per cubic millimetre A return to normal levels does not occur in severely ill patients but the count remains below normal although at a higher level than previously Later eosinopenic episodes are often related to operation or infection and extreme eosinop nia usually returns when a patient is dying.

Pathogenesis.—Eosinopenia is now known to be a sensitive index of adrenocortical hyperactivity (Chapter 18) although the latter probably continues after the post-eosinopenic rise of the count

The ebb and flow of the blood eosinophils is reflected in the number of eosinophils in the spleen (Sevitt, 1955a 1955b) and probably in other organs Eosinopenia is probably produced by a redistribution of the eosinophils throughout the peripheral organs particularly in the reticulo-endothelial system and then destruction follows

Splenic eosinopenia.—Eosinophilia is found in the spleen in those who die within a few hours of burning (Sevitt, 1955b) and may also be found in the liver and lymph nodes of some patients at this period (Bardeen 1898 Wilson, Macgregor and Stewart, 1938) It is a normal phenomenon and is only noticed because the patients die before tissue eosinopenia develops Eosinopenia in the spleen is well established by 24 hours after burning and lasts a few days Since it reflects blood eosinop.nia it may be used as necropsy evidence of recent adrenal hyperactivity

EOSINOPHILIA

This may occur early or later

Early eosinophilia may be found during the post-eosinopenic rise in the eosinophil count that is within a few days of burning (Demidova and her colleagues 1949 Sevitt, 1951) In 4 cases described by Sevitt (1951) the post-eosinopenic rise was exaggerated into an acute episode of eosinophilia and the peak values ranged from 690 to 2,400 per cubic millimetre The count fell until by 7–14 days later it was normal In 2 children the phenomenon was related to streptococcal infection—acute otitis media in one and burn scarlatina in the other probably present at the time of burning

A *late* eosinophilia may develop 4–6 weeks after burning and last for weeks The counts usually range between 600 and 1 500 per cubic millimetre It is a common phenomenon because Sevitt (1951) found it in 5 out of 15 patients (33 per cent) who remained in hospital for

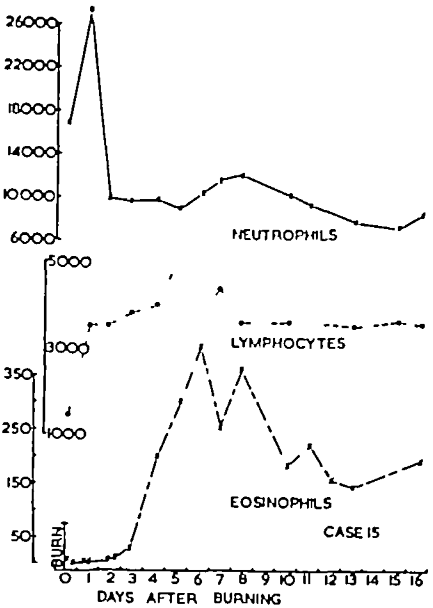


FIG 58 —Serial neutrophil, lymphocyte and eosinophil blood counts from a boy of 2 years with burns involving 20 per cent of the body area The neutrophils show a sharp well-marked leucocytosis after burning (primary wave) and a slight leucocytosis between the sixth and tenth days (secondary wave) There is an early short-lived lymphocytopenia and a considerable eosinopenia lasting 3 or 4 days

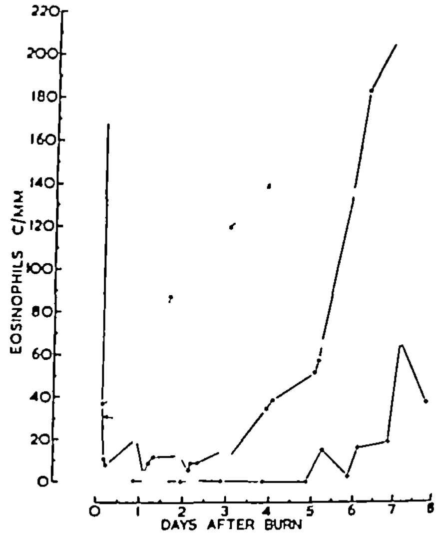


FIG 59 —Eosinopenia after burning Serial blood eosinophil counts in 3 burned patients In one patient the falling of the count soon after burning was detected and this was followed by a period of eosinopenia which is present in all three The eosinopenia lasted 1, 5 and 7 days respectively and was followed by a rise in the count

follow a constant pattern (Fig 59) Within a few hours of burning the number of circulating eosinophils is found to be falling or to have fallen from the normal 100–400 per cubic millimetre usually to between 0–20 and always to below 40 per cubic millimetre Eosinopenia is established a few hours after burning and is maintained for a variable number of days after which the count begins to rise A peak value is reached within a few days and the eosinophil count then declines or returns to normal The pattern therefore is one of post-burn fall, period of eosinopenia, post-eosinopenic rise and later changes

During the post-burn fall the rate of disappearance of eosinophils from the blood is rapid, varying from 30 per cent to 70 per cent of the cells per hour, and the very low values are reached within a few hours The period of eosinopenia lasts 1 or 2 days in patients with burns less than 10 per cent in extent and is longer, usually 3–5 days, in those more extensively burned The end of the extreme eosinopenia is

staining areas containing macrophages (Fig 60) The appearance superficially resembles that seen in central follicular or germinal hyperplasia, but close examination reveals necrosis of the central lymphatic cells Karyorrhexis is in progress and nuclear fragments are found lying free or engulfed by macrophage cells It is the presence of the latter which is largely responsible for the pseudo-hyper plastic appearance The macrophages phagocytose the necrotic cells and sometimes fuse to form foreign body giant cells Later patches of

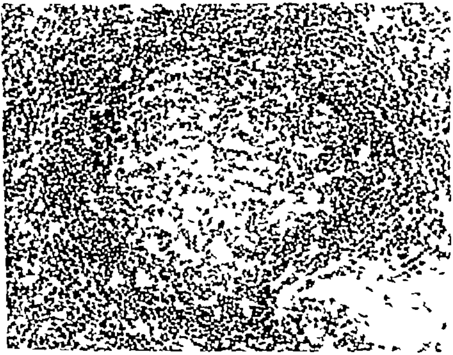


FIG 60 —Malpighian body of the spleen showing central lymphonecrosis From a girl of 4 years who died 15 hours after burns involving 45 per cent of the body area (Haematoxylin and eosin × 200)

homogenous eosinophilic or hyaline material are found in the central part of the follicles and are presumably derived from swelling degeneration and necrosis of the macrophage cytoplasm At this stage nuclear fragments are few or absent The lymphocytes at the periphery of the nodes appear to be normal The lymphonecrotic process is found during the first 3 days and is maximal within 24 hours of burning The phase is succeeded by macrophage degenera tion and by resolution and repair by 7 days after burning abnormal changes are minimal or absent

In adults the process is less apparent irregular and not fully

longer than 28 days Its aetiology is unknown but it might be due to bacterial allergy or to sensitization from a drug used in treatment or possibly from absorption of a skin protein cleavage product

LYMPHOPENIA

Lymphopenia is common after burning Its onset within a few hours is rapid like that of eosinopenia but the degree of fall is moderate and the episode lasts only a day or two The phenomenon is most evident in children (Fig 58) in some of whom the lymphocyte count may temporarily fall to about 1,000 per cubic millimetre In some children there is a considerable fall from initially high levels for example, in one child the lymphocyte count fell from 9,000 per cubic millimetre at 1 hour after burning to 2,500 at 3 hours Often the falling count is not observed but low lymphocyte counts during the first day or two are followed by higher counts on succeeding days, suggesting an early lymphopenia The lymphopenia accompanies the primary neutrophil leucocytosis but the secondary wave of neutrophils may be accompanied by a lymphocytosis The lymphopenia is part of a general body destruction of lymphocytes and like eosinopenia is probably related to adrenocortical hyperactivity (*vide infra*)

TISSUE LYMPHONECROSIS

Changes in the lymphatic system are not restricted to the blood lymphocytes but involve the lymphoid tissue of the whole body A generalized degeneration of lymph nodules rapidly develops during the first few hours after burning The condition was first described by Bardeen (1898) and has been studied by Weiskotten (1919), Fender (1933), Baker (1945), the author and others The lymph nodes and lymphoid tissue become enlarged, swollen and often hyperaemic the tonsils, the cervical, axillary, bronchial and mesenteric nodes, the Malpighian bodies of the spleen, the Peyer's patches of the intestine and the lymphoid cells of Glisson's capsules in the liver are all affected

The changes, which are more apparent in children, are not specific for burns but are found in various infectious diseases such as scarlet fever and diphtheria (Fender, 1933)

The histological changes in children are found within a few hours of burning and last a few days The essential lesion appears to be a degeneration and necrosis of the cells of the central halves of the lymph follicles associated with nuclear fragmentation The changes can be well studied in the Malpighian bodies of the spleen The central areas of these follicles are soon transformed into pale

The divergence in the experience of Brown and Demidova and her colleagues on the one hand and that of the other workers on the other is of interest and might be related to the better intravenous plasma therapy employed. When a reduction in the number of platelets occurs it is unlikely to originate in the bone marrow and must be peripheral in origin It may be that platelets are removed from the circulating blood when certain intravascular changes related to burning are combined with oligaemia In such cases heat precipita tion of fibrin and possibly the sludging of blood may produce capillary thrombosis and embolism and removal of circulating plate lets Conversely maintenance of a relatively normal blood volume and blood flow through the tissues would prevent or reduce the severity of these changes and also the degree of thrombocytopenia.

HYPOPROTHROMBINAEMIA

Campbell Gabriel and Van Hoek (1950) also found a decrease in the plasma prothrombin in their dogs In the animals which subsequently died the prothrombin activity fell sharply to about 40 per cent of normal at 4 hours after burning, but in those which survived there was a slow decline during the first week after an initial slight rise A moderate fall in the plasma prothrombin had previously been reported in burned patients (Wolff Elkington and Rhoads 1940 Holt, Buisseret and Vandenbroucke 1945 Levenson and his col leagues, 1946) Holt and his colleagues found that the lowest values were usually 20–50 per cent of normal and in one patient was as low as 8 per cent. In their experience the low prothrombin persisted for weeks and responded rather slowly to injections of vitamin K The lowered prothrombin could result from the loss of plasma proteins into the burn or from hepatic dysfunction or from both causes (Chapter 22)

FIBRINOGEN

Scalding of rats and dogs caused a marked increase in the plasma fibrinogen (Chanutin and Ludewig, 1947 Campbell Gabriel and Van Hoek 1950) which often doubled or trebled in value A con siderable increase may also occur in burned patients (Prendergast, Fenichel and Daly 1952) Like prothrombin fibrinogen is formed in the liver and it seems strange that the production of the former should be lessened whilst synthesis of fibrinogen is increased

OTHER CLOTTING FACTORS

Little or nothing is known about other factors concerned with clotting In their dogs Chanutin and his colleagues thought there might be a transient depression of accelerator globulin possibly

developed, but some degree of central lymph cell necrosis is often found The different behaviour of the lymphoid tissue of children and adults is not restricted to the changes which follow burning since the lymphatic tissue in children reacts vigorously in many diseases The accentuated change in children parallels the greater degree of acute blood lymphocytopenia found

It is likely that the blood lymphopenia and the tissue lymphonecrosis are part of the same process Bardeen and Weiskotten considered the lymphonecrotic effect in the splenic nodules and elsewhere to be due to burn "toxaemia" just as similar changes in diphtheria were said to result from toxaemia However Dougherty and White (1947) found that blood lymphopenia and tissue lymphonecrosis were regularly produced in animals by injections of ACTH or cortisone It is therefore possible that the whole lymphonecrotic process is the result of the rapid hypersecretion of adrenal cortical hormones, since hyperactivity of the adrenal cortex is known to begin quickly after burning (Chapter 18)

BLOOD PLATELETS AND CLOTTING FACTORS

A variable decrease in the number of blood platelets and a variable fall in the plasma prothrombin commonly follows extensive burning, and not infrequently the plasma fibrinogen rises However the whole blood clotting and bleeding times rarely show any significant abnormality

THROMBOCYTOPENIA

According to Brown (1945) and Demidova and her colleagues (1949) no gross abnormality in the platelet counts of burned patients occurs even in those with large burns Brown, however, noted a tendency for low normal counts during the first 2 weeks and for higher counts subsequently but he implicated local therapy with sulphonamide cream Marked thrombocytopenia was not found On the other hand in 12 out of 13 burned patients studied by MacDonald and his colleagues (1944) a fall in the platelet count was observed 7–57 hours after burning The lowest counts were found at 1–4 days and varied from 9,000 to 96,000 per cubic millimetre Two patients had purpura and in another petechiae were numerous, features unusual in burned patients In burned untreated dogs a progressive thrombocytopenia which commenced immediately after burning was found by Campbell, Gabriel and Van Hoek (1950) The lowest counts, which averaged about one-third of those found before burning, were found about the seventh day

CHAPTER 17

METABOLIC EFFECTS

Loss of weight and a disturbance of nutrition have long been recog nized as common phenomena both after burning and after injury The metabolic reactions are of importance since they involve bio-chemical processes fundamental to life and a complex interplay of endocrine and nervous factors Biochemical studies have revealed alterations in the metabolism of (1) nitrogenous compounds (2) carbohydrates (3) lipoids and (4) vitamins each of which is probably part of an integrated series of responses For convenience how ever the parts have to be considered separately

NITROGEN METABOLISM

PLASMA PROTEINS AND NON PROTEIN NITROGEN

The proteins and the non protein nitrogenous substances of the plasma are altered quantitatively and qualitatively Hypoprotein aemia (Fig 46) and a relative or absolute hyperglobulinaemia may develop soon after burning, mainly because of the loss of plasma proteins particularly albumin into the burn exudate (Chapter 10) Hypoproteinaemia may appear or deepen later not only because there is a further loss of protein from the skin surface but also because body protein is broken down during the katabolic response to injury (*vide infra*) Liver dysfunction has also been invoked in the disturbance Occasionally the fall in the plasma protein level is sufficient to produce oedema

The early abnormality of nitrogen metabolism is also reflected in the slight or moderate temporary azotaemia found during the first few days In absence of renal failure blood urea may rise to 50–60 milligrams per 100 millilitres, the non protein nitrogen level of the plasma increases and there is a temporary elevation in the plasma amino nitrogen polypeptide nitrogen and the undetermined non protein nitrogen fractions (Walker 1945 Harkins and Long 1945 Levenson and his colleagues 1946 Rosenthal and McCarthy 1947 Gefter and Milutskevitch 1949) particularly when burning is extensive The initial oliguria may account for some of the azotaemia but the continuing excess of these substances probably reflects excessive protein katabolism the excessive deamination of amino acids and

followed by an increase They found no significant change in whole-blood clotting time, no evidence of a heparin-like circulating anti-coagulant and no fibrinolytic activity They concluded that there was no marked defect in coagulation after burning although changes occurred in several individual clotting factors

REFERENCES

Baker, R D (1945) *Amer J Path*, **21**, 717

Bardeen, C R (1898) *Johns Hopks Hosp Rep*, **7**, 137

Brown, A (1945) In *Studies of Burns and Scalds*, p 160 M R C Special Report Series No 249

Campbell, D A, Gabriel, L T, and Van Hoek, D E (1950) *Surg Forum*, 515

Chanutin, A, and Ludewig, S (1947) *J Biol Chem*, **167**, 313

Demidova, M N, Maslennikova, G M, and Kachanova, E V (1949) *Khirurgia* No 4, 22

Dougherty, T F, and White, A (1947) *J Lab clin Med*, **32**, 584

Evans, E I, and Butterfield, W J H (1951) *Ann Surg*, **134**, 588

Fender, F A (1933) *Surg Gynec Obstet*, **57**, 612

Holt, J P, Buisseret, J, and Vandenbroucke, J (1945) *C R Soc Biol*, **139**, 86

Levenson, S M, Adams, M A, Green, R W, Lund, C C, and Taylor, F H L (1946) *New Engl J Med*, **235**, 467

Locke, E A (1902) *Boston med surg, J*, **147**, 480

MacDonald, A H, Levenson, S M, Davidson, C S, Tagnon, H J, and Taylor, F H L (1944) *Science*, **99**, 519

McIver, M A (1933) *Ann Surg*, **97**, 670

Prendergast, J J, Fenichel, R L, and Daly, B M (1952) *Arch Surg*, **64**, 733

Schreiner, K, and Puckso, O (1925) *Med Klinik*, **21**, 1882

Sevitt, S (1951) *Brit med J*, **1**, 976

— (1954) *Ibid*, **1**, 541

— (1955a) *J clin Path*, **8**, 42

— (1955b) *J Path Bact*, **70**, 65

Weiner, W, and Topley, E (1955) *J clin Path*, **8**, 324

Weiskotten, H G (1919) *J Amer med Ass*, **72**, 259

Wight, A, Raker, J W, Merrington, W R, and Cope, O (1953) *Ann Surg*, **137**, 175

Wilson, W C, Macgregor, A R, and Stewart, C P (1938) *Brit J Surg*, **25**, 826

Wolff, W A, Elkington, J R, and Rhoads, J E (1940) *Ann Surg*, **112**, 158

nitrogen diminishes and nitrogen is retained this phase of increased anabolism corresponds to the period of repair

The urinary nitrogen during the katabolic phase may reach 2 or 3 times the intake and is associated with an increased excretion of sulphur potassium magnesium and phosphorus In general the ratios of sulphur to nitrogen and phosphorus to nitrogen of the excess excreted indicate that muscle proteins are largely the source of the excess nitrogen sulphur and phosphorus in the urine

The excess nitrogen is predominantly non protein and is mainly in the form of urea but creatinuria has been reported in men and an increased excretion of creatine in burned animals (Clark Peters and Rossiter 1945 Keyser 1948 Gefter and Miluiskevitch 1949) in addition other workers have found a high residual nitrogen fraction Amino aciduria occurs and although its total nitrogen content is small it is theoretically important because it indicates the proteolytic nature of the nitrogen loss By paper chromatography Nardi (1954) identified the amino acids excreted in the urine of 6 extensively burned patients He found up to 10 amino acids in each case, often including essential amino acids like histidine tyrosine glutamic acid and aspartic acid as well as increased amounts of alanine glycine and lysine, which may be present in normal urine The amino aciduria persisted until the burns were healed it accompanied the increased loss of urinary nitrogen and sometimes continued longer Nardi considered that the amino aciduria did not result from an amino acidaemia because the plasma amino nitrogen is only raised for a few days after burning He postulated that the kidneys were respons ible and that the amino acids appeared in the urine because of a failure of tubular absorption

Proteinuria is common in burned patients but is usually slight and transient and can be discounted as a source of nitrogen loss, but exceptionally 0 5 gramme or more may be lost per day Haemoglobinuria may be considerable but is restricted to the first 24–48 hours and does not contribute to the later loss of nitrogen

Factors influencing the degree of nitrogen loss —The amount by which the urinary nitrogen is increased differs considerably from patient to patient and in different reports This is not surprising since the daily excretion depends *inter alia* on the age sex and weight of the patient (males lose more than females) the previous nutritional state the extent and depth of burning and the degree of infection and on the intake of protein and carbohydrate Well nourished patients excrete more nitrogen than previously undernourished subjects in whom nitrogen is more economically used

possibly an impairment of deamination in the liver (*vide infra*) In previously healthy patients blood urea levels above 100 milligrams per 100 millilitres are found only when the burning is extensive and are nearly always the result of renal impairment or renal failure, whether or not the latter is accompanied by oliguria (Chapter 14)

LOSS OF NITROGEN AND NEGATIVE NITROGEN BALANCE

Exudate loss.—In addition to the variable but often considerable protein-rich exudation from the burned surface there is probably an early loss of plasma protein within the burn oedema from katabolism within the swollen tissues Much of the exudate protein is returned to the circulation mainly by the lymphatic stream

The continued or later loss of exudate nitrogen depends on the depth of burning, on rate of healing and on infection The loss from partial skin-loss burns is generally limited to 2 or 3 weeks by which time the skin is epithelialized, but in sloughing and granulating whole skin-loss burns the continued oozing can produce a considerable loss of nitrogen which may continue over weeks or months Most of the loss is as plasma protein but nitrogen is also lost as red blood cells and innumerable leucocytes, particularly if the burn is infected, and of course as necrotic skin The surface loss of nitrogen may be considerable. It can amount to 2–6 grammes per day, it may account for the major part of the negative nitrogen balance and its value may be 25 per cent or more of the urinary nitrogen (Keyser, 1948, Moore and his colleagues, 1950)

Urinary loss.—Burning is followed by a short period of diminished nitrogen excretion which is related to the early oliguria, but within a day or two the output of nitrogen increases considerably and the abnormally high excretion lasts for days or weeks From his studies of the metabolic changes which follow trauma Cuthbertson (1942) related the initial decrease of nitrogen excretion to a lowered metabolic rate due to shock and termed it the "ebb" period of metabolism, but there is no definite evidence that metabolic depression occurs after burning (Chapter 18)

The increased excretion of urinary nitrogen is not peculiar to burned subjects, in whom it was first reported by Davidson (1926), but is also found in injured patients Its metabolic importance was first recognized by Cuthbertson (1930) who later called it the "flow" period of metabolism which he said corresponds to the phase of traumatic inflammation (Cuthbertson, 1942) It is a period of excessive protein katabolism, is associated with an increased oxygen consumption and is accompanied by some fever and increased respiratory and pulse rates—signs of "toxaemia" Later the urinary

nitrogen diminishes and nitrogen is retained this phase of increased anabolism corresponds to the period of repair

The urinary nitrogen during the katabolic phase may reach 2 or 3 times the intake and is associated with an increased excretion of sulphur potassium magnesium and phosphorus In general the ratios of sulphur to nitrogen and phosphorus to nitrogen of the excess excreted indicate that muscle proteins are largely the source of the excess nitrogen sulphur and phosphorus in the urine

The excess nitrogen is predominantly non protein and is mainly in the form of urea but creatinuria has been reported in men and an increased excretion of creatine in burned animals (Clark Peters and Rossiter 1945 Keyser 1948 Gefter and Miluiskevitch 1949) in addition other workers have found a high residual nitrogen fraction Amino aciduria occurs and although its total nitrogen content is small it is theoretically important because it indicates the proteolytic nature of the nitrogen loss By paper chromatography Nardi (1954) identified the amino acids excreted in the urine of 6 extensively burned patients He found up to 10 amino acids in each case, often including essential amino acids like histidine tyrosine, glutamic acid and aspartic acid as well as increased amounts of alanine, glycine and lysine which may be present in normal urine The amino aciduria persisted until the burns were healed it accompanied the increased loss of urinary nitrogen and sometimes continued longer Nardi considered that the amino aciduria did not result from an amino acidaemia because the plasma amino nitrogen is only raised for a few days after burning He postulated that the kidneys were responsible and that the amino acids appeared in the urine because of a failure of tubular absorption

Proteinuria is common in burned patients but is usually slight and transient and can be discounted as a source of nitrogen loss but exceptionally 0 5 gramme or more may be lost per day Haemoglobinuria may be considerable but is restricted to the first 24–48 hours and does not contribute to the later loss of nitrogen

Factors influencing the degree of nitrogen loss —The amount by which the urinary nitrogen is increased differs considerably from patient to patient and in different reports This is not surprising since the daily excretion depends *inter alia* on the age sex and weight of the patient (males lose more than females) the previous nutritional state, the extent and depth of burning and the degree of infection and on the intake of protein and carbohydrate Well nourished patients excrete more nitrogen than previously undernourished subjects, in whom nitrogen is more economically used

Early and adequate transfusion is probably important in diminishing the subsequent katabolic response Flear and Clarke (1955) found that the nitrogen lost in the urine of injured patients who were transfused with blood promptly and adequately was less than the nitrogen lost by those who were undertransfused or who did not receive blood

In patients with relatively restricted burns (up to 10 per cent or even 15 per cent of the body area) the increased loss of nitrogen is relatively small and of short duration whilst in those more extensively burned there is a greater and more prolonged loss Some workers report a considerable daily excretion The patient of Lucido (1940) lost up to 28 grammes of nitrogen per day for 25 days and those of Browne (1942) had an output of this order for several weeks Taylor and his colleagues (1943) found that the excessive loss of urinary nitrogen in 11 out of 22 severely burned patients sometimes amounted to 45 grammes per day, and Moore and his colleagues (1950) estimated that 20–30 grammes were lost daily during the first 20–30 days On the other hand, other workers have found a lesser excretion Cope and his colleagues (1943) reported that the daily loss was not much greater than that which occurred in normal persons and attributed this to the burns being relatively free from infection Anderson and Semeonoff (1945) found a daily *urea* excretion of 30–40 grammes per day (equivalent to about 15–20 grammes of nitrogen) and similar total nitrogen excretions were observed by Keyser (1948)

Negative nitrogen balance—Diets differing considerably in total protein content and calorific value account for some of the variations in urinary nitrogen excretion found by different workers The difference between nitrogen intake and excretion (including faecal and exudate losses) is the nitrogen balance In recently burned and injured patients the balance is negative, that is the loss of nitrogen in the urine, faeces and exudate exceeds the intake in the food The faecal loss is not increased and the negative balance is due to exudate loss and increased excretion in the urine In burned rats the negative balance, all of which was excessive urinary loss, was of the order of 50 milligrams of nitrogen per day (Clark, Peters and Rossiter, 1945) which corresponds to 0 5 gramme per kilogram body weight or about 35 grammes of nitrogen for an average patient This figure is similar to that found by Taylor and his colleagues (1943), but many other workers report considerably lower figures For example, two burned patients studied by Beattie (1947) lost an average of 4 6 and 5 2 grammes of nitrogen daily for 5–7 weeks on a daily diet of 2,750

calories and 100 grammes of protein (16 grammes of nitrogen) Similar or lower negative balances have been reported by others (Moore and colleagues, 1950 Keyser 1948) The difference between some reports is partly artificial because some workers included in the intake the nitrogen in the transfused plasma and blood whilst others have excluded this

The cumulative effect on the body weight of this excessive loss of nitrogen can be considerable Even the negative balances reported by Beattie (1947) which are lower than in many reports amount to a total of about 200 grammes of nitrogen which corresponds to about 8½ pounds (4 kilograms) of muscle To this should be added a loss of fat which takes part in the katabolic process In other reports the actual or calculated wasting was considerably more and some adults lost 2 stones (13 kilograms) or more in weight

Effect of diet—The question whether the negative balance can be reduced or eliminated by dietetic means requires consideration

Increasing the protein content of the diet during the katabolic phase increases the absolute excretion of urinary nitrogen but it is not certain whether the increased loss is equivalent to or less than the increased nitrogen intake In burned patients the matter is more complex than after injury because of the continued exudate loss of nitrogen This is presumably independent of systemic metabolism but on the other hand infection of the burned area which increases the exudate loss may also increase the katabolic urinary loss of nitrogen In burned rats surface loss of nitrogen is unimportant, and Croft and Peters (1945) reported that increasing the dietary protein substantially reduced the tissue wasting and the associated negative nitrogen balance Additional carbohydrate may also be of value because Lathe and Peters (1949) found that it reduced the nitrogen loss in rats in the later part of the katabolic phase Other workers (for example Co Tui and his colleagues 1944) are in agreement with this view and advocate both a high protein intake either as ordinary food or partly as protein hydrolysate as well as a high calorific diet for energy requirements to spare protein breakdown The negative balance has also been attributed to low intake of protein and other foods due to loss of appetite or to the considerable loss of nitrogen from the burned surface, or to both causes Although the theoretical question is not settled it seems logical in clinical practice to commence a high protein/high-calorific diet as soon as possible after burning when there is no evidence of renal failure This is the policy of the Burns Unit in the Birmingham Accident Hospital and the clinical effects are apparently good (Jackson 1956)

When the katabolic phase has ended and the period of anabolism arrives the urinary nitrogen falls and nitrogen is retained in the body for protein synthesis The anabolism is so intense that even the products of local proteolysis are used for rebuilding (Striganova, 1940) All workers agree that it is important to increase the protein and calorific value of the diet at this stage The giving of extra food, even up to 4,000 or 5,000 calories per day and 150 grammes of protein or more to an adult, cannot be overstressed because the increased amount of food determines the rate of nitrogen retention and the rate of muscle rebuilding Convalescence is shortened and the patient returns to normal activity more quickly In many hospitals the diet given to injured and burned patients is quite insufficient and their convalescence is retarded

PATHOGENESIS OF THE KATABOLIC REACTION

Proteolysis and deamination.—As already noted, the evidence of excessive breakdown of body protein is largely based on the increased urinary excretion of nitrogen coupled with a rise in the plasma of the final products of nitrogen metabolism and the appearance of significant traces of intermediate products of protein katabolism. Gefter and Miluiskevitch (1949) argued that if tissue proteinases were increased they may appear in the blood and increase its proteolytic activity They measured *in vitro* the increase of non-protein nitrogen in the blood of burned patients after incubating it at 37°C and found that the increase was significantly greater than that found in normal blood after incubation under the same conditions They attributed this to an increased concentration of blood proteinase which they suggested was an overflow from tissue enzymes

The deaminating power of the normal liver is considerable and is responsible for the very low amino acid content of normal blood and urine even though protein katabolism is continuous and the absorption of amino acids from the bowel into the portal blood is considerable after a protein meal Bekkum and Peters (1951) investigated *in vitro* the deaminating power of the liver of burned rats and found it to be impaired during the period of excessive loss of urinary nitrogen When the liver under test was excised 4 hours after burning, the rate of deamination of DL-alanine was normal but the deaminating power was considerably reduced when the organ was excised and tested 3 days after burning The reduction, which could account for the significant amino acidaemia during the first few days after burning, may be the result of impaired liver function Viewed teleologically it may be a defence mechanism whereby a greater proportion of the amino acids liberated by proteolysis in the muscles

and other tissues is conserved for healing purposes than would be so if the deaminating power were normal

Influence of endocrine glands.—It has been suggested that the excessive protein katabolism is due to excessive secretion of glucocorticoids from adrenal hyperactivity associated with a diminished output of androgens (Albright 1943 Selye, 1946) A similar view was advocated by Campbell and his colleagues (1953) who found experimentally that the increased excretion of urinary nitrogen after implantation of a pellet of cortisone (25 milligrams) was similar to the effect of a single fracture of the femur and the effect of 2 pellets was similar to the effect of 1 pellet plus one fracture However there is now considerable evidence that the protein katabolic response is not determined by an *increased* secretion of adrenal steroids although the phenomenon does not occur in their absence (Ingle, Ward and Kuizenga, 1947 Ingle 1951 Engel 1952 Mason 1955) Ingle found that there was no increase in the excretion of urinary nitrogen after burning adrenalectomized rats, but that when a constant daily dose of adrenal cortical extract was given an increased excretion after burning occurred This was not found in unburned treated controls Similarly Engel showed that the protein katabolic reaction to stress as measured by the rate of increase of the blood urea in nephrectomized animals was abolished by adrenalectomy but it took place when the adrenalectomized animals were given a maintenance dose of cortisone or adrenocortical extract Mason found that a negative nitrogen balance occurred in patients subjected to total adrenalectomy or hypophysectomy when they were maintained on a constant dose of cortisone or corticotrophin respectively Adrenal hormones are therefore necessary but not responsible for the katabolic response to stress, which can take place without an increase in the availability of hormones

Other factors must be responsible for the increased katabolism and one of these may be thyroid function The results reported by Sellers, You and You (1950) in burned rats suggest that the increased nitrogen loss in the urine is significantly reduced but not abolished by previous thyroidectomy whilst Gribble and Peters (1951) found that thyroidectomy largely abolished the excessive loss of nitrogen after burning.

Significance—From a teleological point of view Cuthbertson (1942) suggested that the katabolic impulse was a primitive response essential to the survival of a wounded animal unable to hunt for food The phenomenon was said to be independent of food intake and to take place in order to supply energy or amino acids for the

healing process through proteolysis of muscle and other "labile" stores of protein The process also involves muscle and liver glycogen and the fat depots In support of this concept is the fact that undernourished animals do not exhibit much increase in urinary nitrogen after injury Presumably the amino acids released by proteolysis of muscle are used economically elsewhere in the body for more essential purposes and are not available for deamination The theory of amino acid deficiency was narrowed by Croft and Peters (1945) to specific, essential amino acids They postulated that the proteolysis after burning was necessary to obtain one or more essential amino acids for the healing process Methionine was suggested as a possibility but the earlier hopeful experiments of reducing the negative nitrogen balance by adding methionine to the diet were not confirmed later (*see* page 73)

CARBOHYDRATE METABOLISM

Burning is often followed by an acute rise in the blood glucose, frequently to hyperglycaemic levels, and perhaps by a temporary glycosuria Lactic acidaemia and a fall in the alkaline reserve (carbon dioxide combining power) of the plasma are associated In man post-burn hyperglycaemia has often been reported (Underhill and his colleagues, 1923, Davidson, 1925, McIver, 1933, Lambret, Driessens and Warembourg, 1936, Black, 1940, Anderson and Semeonoff, 1945, Keyser, 1948, and others), whilst the increased glucose and lactic acid in the blood have been studied together by Taylor, Levenson and Adams (1944) and Gefter and Miluiskevitch (1949), and investigations in animals have been reported by Lundberg and Backman (1929), Slocum and Lightbody (1931) and Clark and Rossiter (1944)

HYPERGLYCAEMIA AND LACTIC ACIDAEMIA

The raised blood glucose always appears within a few hours of burning and in animals within an hour generally it is a temporary phenomenon lasting hours or days but in a few patients it continues for a longer period Like many other changes it is more frequent and reaches higher levels in extensively burned patients than in those with lesser burns, but even some of the latter develop hyperglycaemia In 15 of the 35 patients examined by Taylor, Levenson and Adams (1944) the blood glucose was between 163 and 352 milligrams per 100 millilitres within 2 hours of burning and hyperglycaemia developed later in others The mean value on admission calculated from their figures was 107 milligrams per 100 millilitres in 11

patients with burns of less than 10 per cent of the body area compared with 216 milligrams in 13 patients with more than 30 per cent burns Taylor and his colleagues also found a close correlation between the incidence of hyperglycaemia and of haemoconcentration

Similar observations were made by Gefter and Miluiskevitch (1949) who found that the raised glucose values commonly lasted a week On the day of burning 34 per cent of 44 patients had blood glucose levels greater than 150 milligrams per 100 millilitres, between the second and the sixth day similar values were found in 29 per cent of 100 patients but during the second week only 9 per cent of 46 patients had raised fasting levels A considerable proportion of their patients had *low* fasting values later than one month after burning and hypoglycaemic levels of 50–70 milligrams were not infrequent

An acute rise in the blood glucose is not peculiar to burns but occurs after various other injuries haemorrhage dehydration and other conditions

Lactic acidaemia also appears early In man the serial values roughly parallel the blood sugar curve and normal values return by 12–48 hours Blood levels of 6–8 milli-equivalents per litre are common in those extensively burned and higher values have been reported but the high lactic acidaemia which occurs after severe exercise has not been found In rabbits and rats the acute rise in the blood lactic acid is shortlived and normal values return in 3–4 hours The alkaline reserve of the plasma falls as the lactic acid and glucose values rise and estimates below 20 millimols bicarbonate per litre are not uncommon in extensively burned subjects soon after injury The alkaline reserve is also affected by the movement of water and electrolytes and by the transfusion of citrated blood or plasma Gefter and Miluiskevitch thought that the tendency to acidaemia is also brought about through the absorption of acid products of local metabolism from the acutely inflamed skin

PATHOGENESIS

Role of the liver and muscles.—A schematic explanation of the changes which are known and suspected is shown in Fig 61 The immediate source of the raised blood glucose is the liver glycogen (A) In haemorrhagic hyperglycaemia which is analogous to that which occurs after burning, the glucose content of the blood in the hepatic vein of bled cats was found to be considerably greater than that in the heart blood and tying the hepatic vessels before bleeding prevented hyperglycaemia (Schenk 1894 Robertson 1935) Desmarais (1949) found that the post burn increase in the blood glucose was not abolished in partially (65 per cent) hepatectomized rats After

hepatectomy an acute fall in the blood glucose occurred, but when the animals were burned a few hours after operation some elevation of the blood glucose took place but not to a hyperglycaemic level Within a few hours the blood glucose fell below normal, and during the next few days it gradually returned to normal—presumably as regeneration of the liver took place Desmarais believed his experiments indicated that the liver is not the only source of the post-burn hyperglycaemia, on the other hand his hepatectomy was only partial and the post-burn rise in the blood glucose may have been abolished if the whole liver had been removed

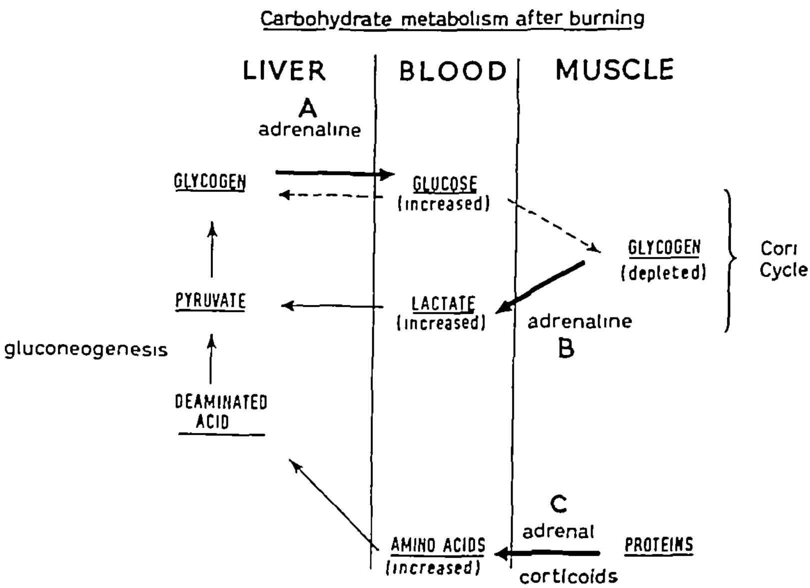


FIG 61 --Diagrammatic representation of the changes in carbohydrate metabolism after burning Heavy arrows indicate increased breakdown, broken arrows indicate impaired activity (*see* text)

The ultimate source of the raised blood sugar is partly from muscle glycogen through its breakdown to lactic acid (Fig 61—B)—hence the lactic acidaemia—and partly from gluconeogenesis from katabolism of proteins in muscle and other tissues (Fig 61—C) Experimental burning of animals is quickly followed by a considerable fall in the carcase and muscle glycogen and this is associated with raised blood lactate and glucose levels (Greenwald and Eliasberg, 1926, Clark and Rossiter, 1944) In the liver the lactate is synthesized to glycogen by way of pyruvate as in the normal Cori cycle (Cori, 1931) The actual liver glycogen content will vary with the previous nutritional state of the animal and on the balance between glycogenolysis induced by adrenaline on the one hand and gluconeogene-

sis by glucocorticoids on the other so that the liver glycogen after burning is not necessarily lowered. Thus Clark and Rossiter (1944) found that rabbits starved for 24 hours and then burned had a lower liver glycogen than the unburned controls, whilst burning produced no change in the liver glycogen of similarly starved and burned rats *In vitro* metabolic studies showed that glycogenolysis by liver brei from burned rabbits was not impaired

Adrenal control—Both the medulla and the cortex of the adrenal gland play a considerable role in producing the metabolic changes The influence on the Cori cycle is mainly due to adrenaline and sympathetic activity (Fig 61—A and B) whilst protein katabolism and gluconeogenesis are largely influenced by adrenocortical secretion (Fig 61—C) Adrenaline is known to be liberated after burning and pharmacologically it produces effects on the blood sugar blood lactate and muscle glycogen similar to those which follow burning. Moreover adrenalectomy before burning considerably reduces all and abolishes some of these changes (Slocum and Lightbody 1931 Clark and Rossiter 1944) but all this effect cannot be attributed to removal of the adrenal *medulla* (*vide infra*) The hyperglycaemia which occurs after head injury can be prevented by previous section of the splanchnic nerves (Mock and de Takats, 1929) and by analogy this supports the other evidence that adrenal medullary stimulation is involved after burning There are however differences between the effects of adrenaline and burning Clark and Rossiter (1944) found that, unlike the effect following burning, the liver glycogen was increased when adrenaline was injected and liver slices from recently burned rabbits had an impaired *in vitro* ability to synthesize glycogen from glucose (Fig. 61—A) compared with the unimpaired glycogenetic power of liver from adrenaline treated animals They attributed this difference to the circulatory changes which follow severe burning

Adrenocortical hyperactivity after burning is associated with an increased secretion and excretion of glucocorticoid hormones such as hydrocortisone which are known to influence carbohydrate metabolism They can cause hyperglycaemia and glycosuria in the fasting animal and an increase in liver glycogen Long (1942) postulated that gluconeogenesis occurred after stress and was associated with the protein katabolic response motivated or permitted by the adrenal cortex. There is strong circumstantial evidence that after deamination of the amino acids which are released by proteolysis the non protein fraction is synthesized in the liver by way of pyruvic acid to glycogen and glucose It is not certain how quickly this occurs and

hepatectomy an acute fall in the blood glucose occurred, but when the animals were burned a few hours after operation some elevation of the blood glucose took place but not to a hyperglycaemic level Within a few hours the blood glucose fell below normal, and during the next few days it gradually returned to normal—presumably as regeneration of the liver took place Desmarais believed his experiments indicated that the liver is not the only source of the post-burn hyperglycaemia, on the other hand his hepatectomy was only partial and the post-burn rise in the blood glucose may have been abolished if the whole liver had been removed

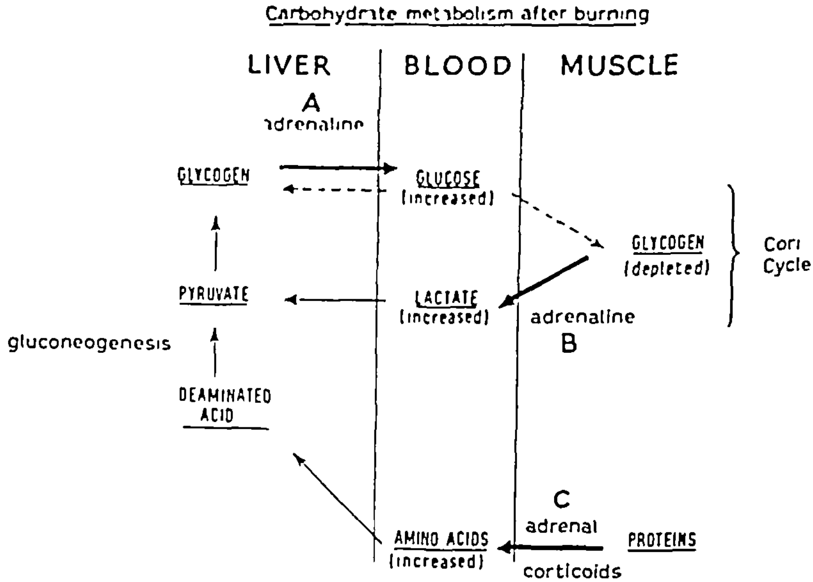


FIG 61 —Diagrammatic representation of the changes in carbohydrate metabolism after burning Heavy arrows indicate increased breakdown, broken arrows indicate impaired activity (*see* text)

The ultimate source of the raised blood sugar is partly from muscle glycogen through its breakdown to lactic acid (Fig 61—B)—hence the lactic acidaemia—and partly from gluconeogenesis from katabolism of proteins in muscle and other tissues (Fig 61—C) Experimental burning of animals is quickly followed by a considerable fall in the carcase and muscle glycogen and this is associated with raised blood lactate and glucose levels (Greenwald and Eliasberg, 1926, Clark and Rossiter, 1944) In the liver the lactate is synthesized to glycogen by way of pyruvate as in the normal Cori cycle (Cori, 1931) The actual liver glycogen content will vary with the previous nutritional state of the animal and on the balance between glycogenolysis induced by adrenaline on the one hand and gluconeogene-

uptake by the body and a decrease in the oxygen content of the venous blood The former may produce and the latter reflect tissue anoxia (Chapter 9) There is also evidence of a disturbance in oxidative reductive processes (Gefter and Miluiskevitch 1949) In some burned subjects even the catalase power of red cells was considerably lowered and for this and other reasons they concluded that cellular oxidative processes were impaired The early lactic acidaemia suggests that the anaerobic breakdown of the glycogen stores is not accompanied by an increase in oxidative metabolic processes through the tricarboxylic cycle

The problem is particularly important because of a possible impairment in cerebral and cardiac metabolism In this connexion the report of Cordier and Dessaux (1950) is of interest they found that the glycogen content of heart muscle was not diminished by extensive burning of rats but was lowered in traumatic shock and they postulated that after extensive burning the heart was unable to utilize its glycogen reserves

BURN DIABETES

In some extensively burned patients the hyperglycaemic state may continue for weeks after which it gradually disappears and in a few patients who subsequently die the blood glucose levels may rise to 500–1 000 milligrams per 100 millilitres This diabetic or pseudo-diabetic state is analogous to but more severe than the prolonged disturbance of carbohydrate metabolism found by Thomsen (1938) in some injured patients In a patient without a history of diabetes it may be difficult to decide whether the condition is due to burning or to exacerbation of subclinical diabetes but the absence of ketonuria and the finding of prolonged hyperglycaemia in previously healthy young children indicates that burning was responsible in at least some of the cases The condition can be exacerbated by a high carbohydrate intake and the patients of Evans and Butterfield (1951) who were fed on high-carbohydrate/high-calorie diets had very high blood glucose levels

The pathogenesis of the diabetic state is not clear but it is likely to be complex, since the hyperglycaemia of some patients is sensitive to insulin whilst in others it is more or less insulin resistant (Butterfield, 1955) Continued diabetogenic over activity of the anterior pituitary and adrenocortical hyperstimulation may play a part but in some patients the pancreas is involved Histological examination of the pancreas of severely burned hyperglycaemic children has shown that some cells in the islands of Langerhans were destroyed or damaged and that others were regenerating (Sevitt, 1955)

how long it lasts gluconeogenesis may be simultaneous with the effects of adrenaline release, but on the other hand it may come into play a little later and prolong the hyperglycaemia initially induced by adrenaline There is also evidence that adrenocortical hormones play a permissive rather than a determining role in carbohydrate metabolism because, among other evidence (Long, Katzin and Fry, 1940), a normal hyperglycaemic response to traumatic shock occurs in adrenalectomized animals treated with adrenocortical extract (Selye and Dosne 1941)

An extra-adrenal influence is also involved because the rise in blood sugar and fall in carcase glycogen after burning is reduced but not abolished by previous adrenalectomy

Nervous control.—Experiments to test the nervous control of the carbohydrate response to burning have not been reported, but Ogata (1936) found that hyperglycaemia after experimental fractures and other limb injuries was prevented by previous section of the nerves to the limb The central connexions of this reflex control are unknown but the efferent path may be through the sympathetic, because, as has already been noted, splanchnicectomy prevents hyperglycaemia after head injury (Mock and de Takats, 1929) It may also be through the activity of the whole peripheral nervous system which, by means of a control of endocrine influence at the tissue level, may modify the metabolic responses to injury (Chorvat, 1955)

Significance.—In their review of the effects of injury on carbohydrate metabolism and energy transformation, Green and Stoner (1954) pose an apparent paradox of shock On the one hand there is a destruction of the carbohydrate stores of the body with which is associated a flooding of the tissues with glucose, and on the other, they say, there is a diminished metabolic rate and energy production They postulate that the hyperglycaemic flood after injury is a defence mechanism whereby the body conserves energy for recovery purposes in face of the increased demands for carbohydrate in the injured area, and they raise the possibility that death in shock is due to the exhaustion of the metabolic stores of a few vital centres

Their thesis is based on the results of animal experiments and it is not certain whether the paradox exists even for untreated burned patients Over-all changes in total body carbohydrate have not been reported and there is disagreement whether the basal oxygen consumption is decreased, unchanged or increased after burning (Chapter 18) On the other hand the circulatory effects of oligaemia result in a decreased carriage of oxygen in the blood, an increase in the *percentage*

The adrenal depletion is related to cortical hyperactivity and may result from a metabolic need for steroid synthesis and oxidation It can account for only a little of the total vitamin retention

OTHER VITAMINS

A decreased urinary excretion of thiamine nicotinic acid and riboflavin has been reported and may result from an increased demand by the tissues Detailed reports are lacking.

REFERENCES

Albright, F (1943) *Harvey Lectures* 38, 123
Anderson, A. B and Semeonoff E. (1945) In *Studies of Burns and Scalds* M.R.C Special Report Series No 249
Beattie J (1947). *Brit med J.*, 2, 813
Bekkum, D W van, and Peters, R. A (1951) *Quart J exp Physiol.*, 36, 1951
Black D A K (1940) *Brit med. J.*, 2, 693
Browne, J S. L. (1942) In *Report on Bone and Wound Healing* p 50 Second Meeting, Josiah Macey Jr Foundation.
— (1951) In *Symposium on Burns*, p 105 National Research Council, Washington, D C.
Butterfield, W J H. (1955) *Lancet* 1 489
Campbell, R. M Sharp G M E. Boyne, A. W and Cuthbertson, D P (1953) *Nature* 172, 158
Chorvat, J (1955) *S C R. Soviet med Bull.*, 2, 17
Clark, E. J., and Rossiter R. J (1944) *Quart J exp Physiol* 32, 269 279
— Peters, R A., and Rossiter R. J (1945) *Ibid.*, 33, 113
Cope, O., Nathanson, I Rourke G M and Wilson H (1943) *Ann Surg* 117 937
Cordier D., and Dessaux, G (1950) *C R. Soc Biol.*, 145, 397
Cori, C. F (1931) *Physiol Rev* 11 143
Co Tui, Wright, A. M., Mulholland, J H., Barcham, I., and Breed, E. S (1944) *Ann. Surg.*, 119 815
Croft, P B., and Peters, R. A. (1945) *Lancet* 1, 266
Cuthbertson, D P (1930) *Biochem. J.*, 24, 1244
— (1942) *Lancet* 1 433
Davidson, E. C. (1925) *Surg Gynec Obstet.*, 41 202.
— (1926). *Arch Surg* 13 262.
Desmarais, A. (1949) *Laval Medical* 14 346
Engel F L. (1952) *Endocrinology* 50 462.
Evans, E. I., and Butterfield, W J H (1951). *Ann Surg* 134, 588
Flear C T G., and Clarke, R. (1955) *Clin Sci* 14 575
Gefter I M and Milulskevitch, G F (1949) *Khirurgia*, No 4 26
Green, H N., and Stoner, H. B (1954) *Brit med. Bull.*, 10 38
Greenwald H M., and Eliasberg, H (1926) *Amer J med. Sci* 171 682.
Gribble M de G and Peters, R. A (1951) *Quart J exp Physiol* 36, 119
Harkins, H N and Long, C. N H. (1945) *Amer J Physiol.*, 144 661
Ingle D J (1951). In *Recent Prog Hormone Res* 6, 159
— Ward, E. O., and Kuizenga, M H (1947) *Amer J Physiol* 149 510
Jackson, D McG (1956). Personal communication
Keyser J W (1948) *Ann Surg.*, 127 605
Lambret, O Driessens, J., and Warembourg, H (1936) *C R Soc Biol.*, 123, 10
Lathe G H., and Peters, R. A. (1949) *Quart J exp Physiol* 35, 55
Levenson, S M., Adams, M A., Green, R. W., Lund, C C and Taylor F H L (1946). *New Engl. J Med.*, 235, 467

Effect of burning on diabetes mellitus—The hyperglycaemia and glycosuria are increased, ketonuria occurs and the insulin requirement is augmented

FAT AND LIPOIDS

Tissue wasting in burned patients involves the subcutaneous and other fat depots but nothing is known of the metabolic process Ketonuria is usually absent or slight

Patients who die later than a week or two after burning commonly have a fatty liver and Monsaingeon (1952) was impressed by the association of this "steatose hepatique" with tissue wasting and nitrogen loss A similar fatty change occurs during starvation and various kinds of malnutrition so that the fatty liver in burned patients might have a nutritional basis Analysis of the fat extracted from a number of livers at necropsy has shown that a high content of cholesterol esters is often present

Decrease of the adrenocortical cholesterol and other lipoids occurs as a result of glandular hyperactivity presumably because they are a labile store of steroid

Electrophoretic studies of the plasma of burned patients has shown an abnormality in the plasma lipoprotein (Ricketts, 1955) the significance of which is unknown

VITAMINS

ASCORBIC ACID

Burning induces a fall in the ascorbic acid content of the blood and a considerable reduction in its urinary excretion even when the previous intake was adequate (Gefter and Miluiskevitch, 1949, Browne, 1951) Saturation tests of burned patients indicate a considerable utilization of the vitamin because an intake of 0 5 gramme or more per day is not followed by a rise in the blood or urine levels Adrenocortical hyperactivity is not responsible for this because ascorbic acid retention does not follow administration of ACTH The subsequent demand of the burned area for ascorbic acid, which is needed for dermal regeneration (Chapter 4), is also unlikely to account for all the vitamin retention Presumably metabolic needs for oxidative purposes are determinant Because of this extra metabolic demand most workers advocate giving extra vitamin C to burned patients

The ascorbic acid content of the adrenals of rabbits also diminishes rapidly after burning, but in the liver there is no fall and possibly a slight increase in the vitamin content (Clark and Rossiter, 1944)

The adrenal depletion is related to cortical hyperactivity and may result from a metabolic need for steroid synthesis and oxidation It can account for only a little of the total vitamin retention

OTHER VITAMINS

A decreased urinary excretion of thiamine nicotinic acid and riboflavin has been reported and may result from an increased demand by the tissues Detailed reports are lacking

REFERENCES

Albright, F (1943) *Harvey Lectures* 38, 123
Anderson, A. B and Semeonoff E. (1945) In *Studies of Burns and Scalds* M.R.C Special Report Series No 249
Beattie, J (1947). *Brit med. J* 2, 813
Bekkum, D W van, and Peters, R. A (1951) *Quart J exp Physiol* 36, 1951
Black, D A K. (1940) *Brit med. J.*, 2, 693
Browne, J S L. (1942) In *Report on Bone and Wound Healing* p 50 Second Meeting, Josiah Macey Jr Foundation.
— (1951) In *Symposium on Burns* p 105 National Research Council, Washington, D C.
Butterfield, W J H. (1955) *Lancet*, 1 489
Campbell, R. M Sharp G M. E., Boyne A. W and Cuthbertson D P (1953) *Nature* 172, 158
Chorvat, J (1955) *S C R. Soviet med Bull* 2, 17
Clark, E. J and Rossiter R. J (1944) *Quart J exp Physiol.*, 32, 269 279
— Peters, R. A., and Rossiter R. J (1945) *Ibid.* 33, 113
Cope O., Nathanson, I., Rourke, G M., and Wilson, H (1943) *Ann. Surg* 117 937
Cordier D and Dessaux, G (1950) *C R. Soc Biol* 145, 397
Cori, C. F (1931) *Physiol Rev* 11 143
Co Tui, Wright, A. M Mulholland, J H Barcham, I., and Breed, E. S (1944) *Ann. Surg.*, 119 815
Croft, P B. and Peters, R. A. (1945) *Lancet* 1, 266.
Cuthbertson, D P (1930) *Biochem J.*, 24, 1244
— (1942) *Lancet* 1 433
Davidson, E. C. (1925) *Surg Gynec Obstet* 41 202.
— (1926) *Arch. Surg* 13 262.
Desmarais, A. (1949) *Laval Medical* 14, 346
Engel, F L. (1952) *Endocrinology* 50, 462.
Evans, E. I. and Butterfield, W J H. (1951) *Ann Surg* 134, 588
Flear C T G., and Clarke, R. (1955) *Clin Sci*, 14 575
Gefter I M., and Miluskevitch, G F (1949) *Khirurgia*, No 4 26
Green, H N and Stoner, H B (1954) *Brit med. Bull.* 10, 38
Greenwald, H. M., and Eliasberg, H (1926) *Amer J med. Sci.* 171 682.
Gribble, M de G and Peters, R. A. (1951) *Quart J exp Physiol* 36, 119
Harkins, H N and Long, C. N H (1945). *Amer J Physiol.*, 144 661
Ingle D J (1951) In *Recent Prog Hormone Res* 6, 159
— Ward, E. O., and Kuizenga M H (1947) *Amer J Physiol* 149 510
Jackson, D McG (1956) Personal communication.
Keyser J W (1948) *Ann. Surg.*, 127 605
Lambret, O Driessens, J., and Warembourg, H (1936) *C R. Soc Biol* 123, 10
Lathe G H., and Peters, R. A. (1949) *Quart J exp Physiol* 35 55
Levenson, S M., Adams, M A., Green R W Lund, C C and Taylor F H L (1946). *New Engl. J Med.*, 235, 467

Long, C N H (1942) *Endocrinology*, **30**, 870
— Katzin, B, and Fry, E G (1940) *Ibid*, **26**, 309
Lucido, J (1940) *Ann Surg*, **111**, 640
Lundberg, H, and Backman, E L (1929) *C R Soc Biol*, **101**, 931
McIver, M A (1933) *Ann Surg*, **97**, 670
Mason, A Stuart (1955) *Lancet*, **2**, 632
Mock and de Takats (1929) Quoted by Thomsen, V (1938)
Monsaingeon, A (1952) *Mem Acad Chir*, **6 & 7**, 197
Moore, F D, Langohr, J L, Ingebretson, M, and Cope, O (1950) *Ann Surg*, **132**, 1
Nardi, G L (1954) *J clin Invest*, **33**, 847
Ogata, T (1936) *Arch klin Chir*, **187**, 19
Ricketts, C R (1955) Personal communication
Robertson, J D (1935) *J Physiol*, **84**, 393
Rosenthal, O, and McCarthy, M D (1947) *J clin Invest*, **26**, 827
Schenk, F (1894) *Pflug Arch*, **57**, 553 Quoted by Clark and Rossiter (1944)
Sellers, E A, You, S S, and You, R W (1950) *Endocrinology*, **47**, 148
Selye, H (1946) *J clin Endocrin*, **6**, 117
— and Dosne, C (1941) *Proc exp Biol med*, **48**, 532
Sevitt, S (1955) *Lancet*, **1**, 566
Slocum, M A, and Lightbody, H B (1931) *Amer J Physiol*, **96**, 35
Striganova, A (1940) *C R Acad Sci U S S R*, **27**, 385
Taylor, F H L, Levenson, S M, and Adams, M A (1944) *New Engl J Med*, **231**, 437
— — — Davidson, C S, and McDonald, H (1943) *Science*, **97**, 423
Thomsen, V (1938) *Acta med scand suppl*, **91**
Underhill, F P, Carrington, G L, Kapsinow, R, and Pack, G (1923) *Arch intern Med*, **32**, 31
Walker, J (1945) *Amer J med Sci*, **209**, 413

CHAPTER 18

ENDOCRINE RESPONSES TO BURNING

THE reactions to skin burning of (1) the anterior pituitary (2) adrenal cortex, (3) adrenal medulla, (4) posterior pituitary and (5) the thyroid gland are considered here

The recent availability of ACTH and cortisone stimulated an interest in the pituitary gland of burned and injured subjects and renewed the older interest in the adrenal cortex It is now known that burning is rapidly followed by a hyperactivity of the anterior pituitary and adrenal glands which may last for days or longer Secretion of adrenocorticotrophic hormone of the pituitary (ACTH) stimulates the adrenal cortex to secrete various hormones which produce or permit various peripheral effects Hyperadrenalinaemia also occurs and some workers claim there is a period of thyroid hyperactivity Nothing is known of parathyroid activity

ANTERIOR PITUITARY

The adrenocorticotrophic secretion of this gland is under nervous control *via* the hypothalamus probably through a hormone secreted by the hypothalamus into the hypophyseal portal blood supply (de Groot and Harris 1950 Hume and Wittenstein 1950) The system is activated by two processes, neural and adreno-medullary (Fig 62) Hume and Wittenstein showed that the hypothalamic adrenocorticotrophic stimulation can be induced by nervous stimuli from an injured area and that the afferent reflex path passes through the spinal cord this is obviously of significance in burns The remainder of the reflex path is unknown but frontal hypothalamic connexions may be involved since the frontal lobe is now recognized as the head ganglion of the autonomic nervous system and anatomical connexions to and from the hypothalamus are now established (*see* Fulton 1948)

Intravenous adrenaline increases the adrenocortical activity (Vogt, 1944) Adrenaline acts mainly by stimulating the production of ACTH (Long and Fry 1945) and possibly also through a direct action on the adrenal cortex (Speirs and Meyer 1949) The chief site of action of adrenaline is uncertain it may be the adenohypophysis (McDermott and his colleagues, 1950) or above this level possibly the hypothalamus

MORPHOLOGICAL CHANGES

In fatally burned subjects the anterior pituitary is swollen and hyperaemic, particularly in those who die within a few days of burning

Cytochemical changes were studied by Symington and his co-workers following the suggestion of Pearse (1952) that degranulation of the periodic acid-Schiff-positive mucoid cells (mainly basiphils) was an index of secretory activity (Currie and Symington, 1955a,

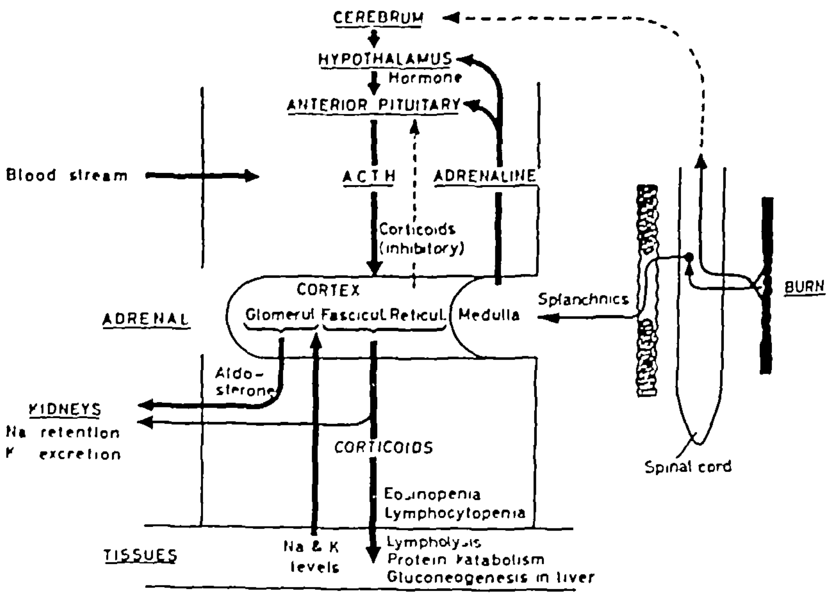


FIG 62 —Diagrammatic representation of the pathways involved in the secretion of ACTH and adrenal hormones after burning and of the hormonal effects The neural-hypothalamic-anterior pituitary pathway to adrenocortical hyperactivity is probably more important than the splanchnic-adrenal-medullary mechanism Aldosterone secretion by the zona glomerulosa influences sodium and potassium excretion by the kidneys Secretion of aldosterone is probably controlled either by the sodium and potassium levels in the tissues or by changes in blood volume

1955b, Symington and his colleagues, 1955) They found that the relative number of degranulated cells was increased in fatally burned subjects and in others subjected to recent stress With few exceptions cytological degranulation was associated with adrenals presenting depletion of cortical lipoid Marshall (1951) showed that ACTH is localized to the basiphil cells and Symington and his colleagues suggested that mucoid cell degranulation was the morphological basis of ACTH secretion A reduction in the number of basiphil cells in the human and dog pituitary after burning was found by Shanklin (1956) who also noted the loss and degranulation of cells using the periodic-acid-Schiff technique

Changes in the acidophil and chromophobe cells have also been reported, but their significance is unknown Shanklin found a prominence of the acidophil granules in the central part of the gland whilst at the periphery many acidophil and chromophobe cells were in various stages of degeneration A marked increase in the acid haematin stainable cytoplasmic granules of the rat acidophils was described by Finerty Hess and Binhammer (1952)

ADRENAL CORTEX

The three main groups of adrenocortical hormones are (1) hydrocortisone (11–17 hydroxycorticosterone) and possibly other steroids with similar properties (S-hormones) (2) androgens (testoids, sex hormones N hormone) and (3) aldosterone or mineralocorticoid hormone Hydrocortisone may be considered typical of the hormones responsible for eosinopenia and lymphocytopenia and influencing carbohydrate and nitrogen metabolism (protein katabolism or anti anabolism) the androgens affect the secondary sexual characters but also exert an anabolic influence on protein metabolism whilst aldosterone is probably responsible for most of the adrenal power to retain sodium and chloride, although this property appears to be shared by other hormones including hydrocortisone

The main hormone secreted under the influence of ACTH is hydrocortisone (Pincus, Hechter and Zaffaroni 1951) but androgen production may also be increased Secretion of aldosterone, although increased by ACTH mainly depends on the salt levels of the blood and tissues and appears to be independent of the pituitary (Singer and Stack Dunne 1955 Dixon 1955) (Fig 62) Both hydrocortisone and androgens are secreted by the zonae fasciculata and reticularis but the zona glomerulosa is said to produce aldosterone

HYPERACTIVITY AND HYPERSECRETION

Hypersecretion of the adrenal cortex is believed to occur because many of the effects of burning resemble the pharmacological actions of ACTH or cortisone (Table II) In the blood a profound eosinopenia a moderate lymphocytopenia and a neutrophil leucocytosis develop within a few hours of burning (Figs 58 and 59) and after administration of ACTH or cortisone Degenerative changes in lymphoid tissue are found in fatally burned patients (Fig 60) and develop after the injection of ACTH Similar disturbances of carbohydrate metabolism including hyperglycaemia, occur in burned subjects and animals and after administration of ACTH or cortisone Similar changes in nitrogen metabolism such as increased nitrogen excretion follow burns and the giving of ACTH and 11-oxysteroids Sodium and chloride retention and free excretion of potassium occur

during the first few days after burning and after injections of ACTH, cortisone, desoxycorticosterone, and particularly aldosterone The plasma corticosteroid level is raised and the urinary excretion of 17-ketosteroids, biologically active reducing glycocorticoids and other corticosteroids is increased after burning and after administration of ACTH to animals or man Furthermore similar histological changes are found in the adrenal cortex after burning and after injection of

TABLE II

Comparison of haematological, metabolic and other changes after burning with those following the administration of ACTH and/or cortisone

	After burning (1)	*After ACTH or cortisone* (2)	*Authors*
Eosinopenia, lymphocytopenia and neutrophil leucocytosis	Yes	Yes	(1) *See* Chapter 16 (2) Thorn, Prunty & Forsham, 1947a, Dougherty & White, 1947, Hills, Forsham & Finch, 1948
Lymphoid tissue	Degeneration	Degeneration	(1) *See* Chapter 16 (2) Dougherty & White, 1947
Blood glucose	Raised	Raised	(1) *See* Chapter 17 (2) Forsham & his colleagues, 1948, Conn, Louis & Johnson, 1949
Urinary excretion of nitrogen	Increased	Increased	(1) *See* Chapter 17 (2) Long, Katzin & Fry, 1940, Sprague & his colleagues, 1950
Sodium and chloride excretion in the urine	Decreased	Decreased	(1) *See* Chapter 13 (2) Prunty, Forsham & Thorn, 1948
Potassium excretion	Free	Free	(1) *See* Chapter 13 (2) Prunty, Forsham & Thorn, 1948
Urinary 17-ketosteroids and corticosteroids	Increased	Increased after ACTH	(1) Cope & his colleagues, 1943, Heard, Sobel & Venning, 1946, Tompsett & Oastler, 1947, Wardlaw, 1950, Evans & Butterfield, 1951 (2) Thorn, Prunty & Forsham, 1947b, Venning & his colleagues, 1948, Prunty, 1950
Adrenal ascorbic acid	Decreased	Decreased after ACTH	(1) Clark & Rossiter, 1944 (2) Long, 1947, Sayers & Sayers, 1949
Adrenal cholesterol	Decreased	Decreased after ACTH	(1) Harkins & Long, 1945 (1) & (2) Long, 1947
Adrenal lipoid	Decreased	Decreased after ACTH	(1) Pfeiffer, 1919–20, Nakata, 1925, Crema, 1928, Bekauri, Danilov & Moissejeff, 1944, Delarue, Monsaingeon & Laumonier, 1950, Symington & his colleagues, 1955, Sevitt, 1955 (2) Symington, Duguid & Davidson, 1955

ACTH The ascorbic acid content of the adrenals in burned rats is reduced and a similar loss occurs when ACTH is given while the cholesterol content of the adrenals in rats is decreased both after burning and after ACTH Harkins and Long (1945) showed that this was mediated through the pituitary because prior hypophysectomy of the rats prevented the post burn cholesterol loss in the adrenals A depletion of extractable and histologically stainable cortical lipoid is found in burned animals and in patients treated with ACTH

It may be concluded that the adrenal cortex is actively stimulated after burning through an increased production of ACTH by the anterior pituitary however it is doubtful whether all the above effects can be solely attributed to hormonal activity (*vide infra*)

The quality and duration of adrenocortical hypersecretion can be roughly assessed from (1) the plasma corticosteroid levels, (2) the urinary excretion of steroids, (3) the duration of eosinopenia and (4) depletion of lipoid in the adrenal cortices

Plasma corticosteroid level—Plasma levels of 17 hydroxycorticosteroids were reported by Hume, Nelson and Miller (1956) in a group of burned men and were correlated with urinary excretion During the first 2 weeks the plasma levels and urinary excretion were increased, particularly in the more extensively burned patients after which there was a return to normal Hume and his colleagues noted that not infrequently the plasma level of free corticosteroid was high whilst the urinary excretion which was in the conjugated form was low Later complications were often associated with increased levels

Urinary steroids.—The relationship of the steroids excreted to the hormones secreted is poorly understood and probably varies under different conditions Apart from the amount excreted from testicular secretion most of the urinary 17 ketosteroid probably reflects the secretion of adrenal androgens and urinary corticosteroids (termed according to the method of estimation neutral reducing corticoids 11-oxysteroids "formaldehydrogenic corticoids 17 hydroxy-corticosteroids and biologically assayable glucocorticoids) are mainly from the secretion of hydrocortisone

17 ketosteroids—The excretion of 17 ketosteroids during the first few days after burning is greater than subsequently and is maximum about the second or third day (Cope and his colleagues 1943 Wardlaw 1950 Evans and Butterfield 1951) Often the early excretion is greater than normal but it rarely exceeds 20–30 milligrams per day and will fall to 10 milligrams or less during the following week or so Sometimes the early excretion is within normal limits

and subsequently below normal, but in other cases the output may be low throughout Fluctuations between relatively high and relatively low daily excretions are often associated with variations in the excretion of nitrogen Early excessive excretion appears to be inconsistent with the negative nitrogen balance during this period because androgens, from which the 17-ketosteroids were presumably derived, have an anabolic effect on protein metabolism On the other hand androgenic influence may be counterbalanced by a greater secretion of hydrocortisone, which has a katabolic effect

Corticosteroids —Excessive excretion of corticosteroids is common after burning particularly in extensively burned persons (Heard, Sobel and Venning, 1946, Tompsett and Oastler, 1947, Talbot and his colleagues, 1947, Evans and Butterfield, 1951, Browne, 1951, Hume, Nelson and Miller, 1956) The increased excretion may last for 2 weeks or so, longer than that of the 17-ketosteroid excretion, and there may be significant day-to-day fluctuations in the amount excreted which may represent intermittent phases of increased hydrocortisone secretion Some workers have suggested that there is a reciprocal relationship between the amounts of 17-ketosteroids and corticosteroids excreted, and by inference between androgenic and hydrocortisone secretion, but this has not been established

Implications —Thorn (1951) considered that the fall in the urinary output of steroids a few days after burning was the result of an absolute or relative deficiency of adrenal secretion, and thought that therapy with ACTH or cortisone might be beneficial This is doubtful, first because a decreased excretion of corticoids may coexist with a raised plasma level (Hume, Nelson and Miller, 1956), secondly because decreased excretion may be associated with adrenocortical hyperactivity, and thirdly because there is no evidence that excessive hypersecretion is a beneficial phenomenon On the contrary it can be a most ominous sign The plasma corticoid level may be very high in patients who subsequently die (Hume, Nelson and Miller, 1956), and evidence of adrenocortical hyperactivity is almost constantly found in fatally burned and injured patients (Sevitt, 1955) although this does not mean that it contributes to death

Duration of eosinopenia —An indirect index of adrenal hypersecretion is the spontaneous post-burn eosinopenia, the duration of which represents the minimum period of glandular hyperactivity From a study in 35 patients Sevitt (1951, 1954) found that the eosinopenia lasted only 1 or 2 days in patients with burns involving less than 10 per cent of the body area and was more prolonged, usually 3–5 days, in those more extensively burned In very ill patients the

eosinophil count remained low for weeks although at a higher level than in the immediate post burn period The period of eosinopenia is generally shorter than the period of increased corticoid excretion The post-eosinopenic increase of the blood eosinophils does not necessarily mean a cessation of hyperactivity because it is well known that after an early phase of eosinopenia the blood eosinophils escape to normal levels in patients on continued cortisone or ACTH therapy Intermittent eosinopenic episodes are not infrequent during the course of the burn illness they probably reflect episodes of increased adrenal activity and can often be related to operations dressings infection or other causes of stress

Other difficulties of interpretation face an analysis based on alterations in salt, carbohydrate and particularly nitrogen metabolism in each of which cortical hormones are involved because the metabolic changes do not necessarily reflect an increased secretion of adrenal hormones (*vide infra*)

Cortico-lipoid depletion.—The remaining source of evidence is in the glands of burned subjects who die at different times Almost constantly there is a partial or complete depletion of cortical lipoid in those who succumb days or weeks after burning (Figs 64–66) and this can nearly always be correlated with eosinopenic evidence of adrenocortical hyperactivity (Sevitt, 1955) However those who die do not necessarily represent the majority who survive although they may be typical of those who are very ill

PERMISSIVE ROLE OF ADRENAL HORMONES

This concept is noted elsewhere with regard to sodium and chloride retention (Chapter 13) and the protein katabolic impulse and gluconeogenesis after burning and injury (Chapter 17) In brief the adrenal hormones are *necessary but not responsible for these phenomena* The electrolyte and metabolic reactions to stress do not occur in adrenalectomized or hypophysectomized animals so that the adrenal hormones are essential but when such animals (or patients) are maintained on a *constant* but adequate dose of cortisone or ACTH respectively the electrolyte and metabolic responses to stress are similar to those which occur *in similarly stressed intact animals* and man Thus adrenal hormones play a permissive role in the altered metabolism without the hormones the biochemical reactions to injury do not occur but they can take place without an increase in their availability

There must be an additional explanation for the metabolic and biochemical effects here nervous activity may be involved and the

dual neuro-humoral concept postulated by Chorvat (1955) is attractive He explained the well-known trophic influence of the nervous system by postulating that the metabolic reactions of organs and tissues to hormones are influenced by their nerve supply, and that stimulation and inhibition of nerve endings modify the biochemical reactions to humoral factors It is possible that the various biochemical and metabolic disturbances which follow burning are provoked by a dual nervous-adrenal hormone mechanism

MORPHOLOGICAL CHANGES

The adrenals in fatally burned patients are usually congested and swollen, particularly in children, the cortices being thickened and

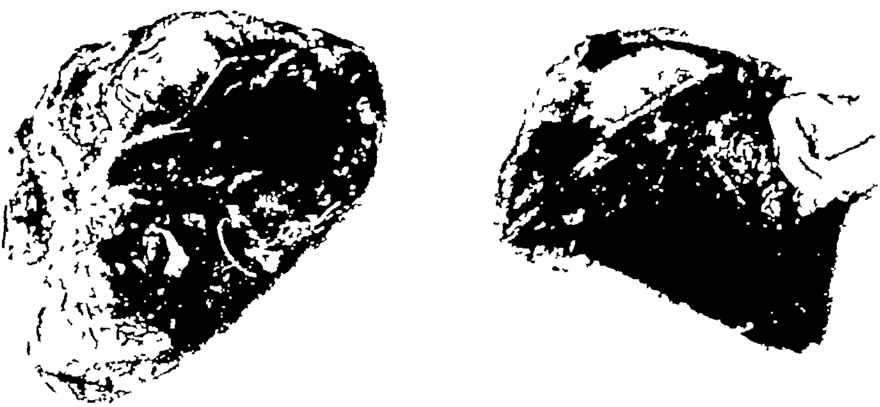


FIG 63 —Dark, reddish-black swollen adrenal glands from a girl aged 4 years who died 7 days after extensive burning The congested appearance was accentuated by the absence of opaque yellow lipoid in the cortex

hypertrophied and the glands perhaps twice the normal weight The vascular and hypertrophic changes become established about 24 hours after burning and are slight in those who die earlier

Haemorrhage—Capillary haemorrhages are common both in the cortex and in the medulla and may locally destroy the parenchyma, but the amount of tissue affected is only a fraction of the whole Rarely the cortical haemorrhages coalesce and involve most of the cortex but this was found in only 2 out of 82 autopsies studied by Sevitt (1955) Even then hypersecretion may be taking place, since in one of these subjects splenic eosinopenia was extreme, which suggested that the remaining viable cortex was sufficient to produce hyperactivity True adrenal apoplexy in which a central blood clot distends the surrounding cortex has occasionally been described

(for example by Harris, 1929) but it is very rare and usually uni lateral

Degenerative changes.—Various other changes may be found in the cortex (Sevitt, 1955 Symington and Davidson 1956) These include foci of necrosis without haemorrhage which had been earlier described by Weiskotten (1917 1919) areas or groups of cells showing considerable hydropic ballooning to the point of disruption (Fig 67) irregular rupture of cells oedema between the columns of the zona fasciculata and a pseudo-acinous or pseudo-tubular change in this zone

In the latter the solid columns of the fasciculata are transformed into acinous or tubular like structures by lysis of the central cells, and are sometimes separated by an inflammatory exudate Rich (1944) described this change in various severe infections including diphtheria and postulated a relationship between it and the circulatory collapse of some patients Many burned patients who die later than 24 hours after injury show a slight or considerable degree of pseudo-acinous degeneration (Fig 68) The change is independent of lipoid depletion since it may be found when the affected areas of the fasciculata are either filled with or are depleted of lipoid The significance of pseudo-acinous degeneration was investigated by Sevitt (1955) who found that most of the patients had splenic eosinopenic evidence of adrenocortical hyperactivity It was concluded that Rich s postulate of a relationship between pseudo-acinous degeneration and circulatory collapse cannot be accepted since this would imply that failure or exhaustion of the gland had occurred The origin of the condition is uncertain but it is probably related to hyperaemia oedema and cellular activity in the cortex

Cortical lipoid depletion.—The normal resting adrenal cortex contains abundant sudanophil lipoid especially in the zonae glomerulosa and fasciculata Loss of lipoid occurs after burning, and its extent and significance was investigated by Symington and his co-workers (Symington and his colleagues, 1955 Symington and Davidson 1956) and by Sevitt (1955) The earliest loss of lipoid was generally found in the zona reticularis and the inner part of the fasciculata but sometimes a regular or focal depletion of the glomerulosa also occurred This suggested that it has an independent secretion and the loss of lipoid here may represent secretion of aldosterone At first the inner lipoid loss extended evenly and presented an even picture of inner zone loss (Fig 64) further loss was irregular and patchy and although most of the lipoid was depleted from the inner half or two-thirds of the cortex irregular alternation of lipoid-depleted and

FIG 64

FIG 66

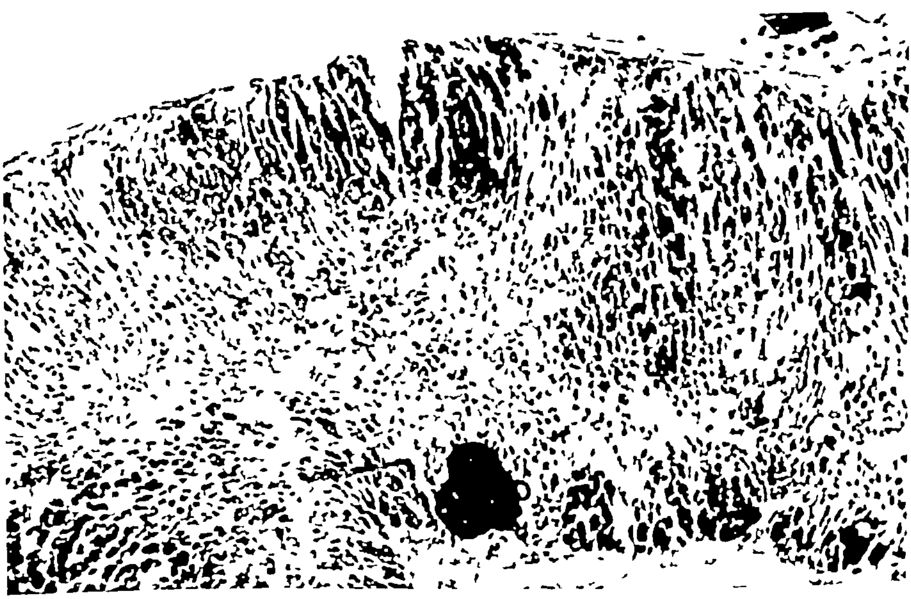


FIG 65

FIGS 64–66 —Frozen sections of adrenal glands, from 3 fatally burned patients, stained with Sudan IV or oil red O and lightly counterstained Heavy black indicates lipoid FIG 64 —Lipoid depletion is confined to the zona reticularis and the inner part of the zona fasciculata (× 44) FIG 65 —Considerable but irregular loss of lipoid with patchy lipoid-containing foci alternating irregularly with depleted areas (× 30) FIG 66 —Almost total depletion of cortical lipoid (× 60)

lipoid filled areas involved the fasciculata (Fig. 65) In other glands, particularly those from burned children dying later than 24 hours after burning there was no lipoid in the cortex or merely a few small isolated foci confined to the glomerulosa or the outer fasciculata (Fig. 66) In the glands of some subjects the *outer* half of the cortex

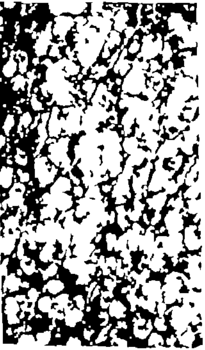


FIG 67.—Ballooning of adrenocortical cells. The hydropic change has grossly distended the cytoplasm sometimes to the point of rupture. (Haematoxylin and eosin × 130)

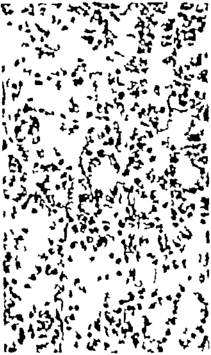


FIG 68.—Pseudo-acinous degeneration of the adrenal cortex in a burned patient. The solid columns of the zona fasciculata are transformed into hollow pseudo-acinous or pseudo-tubular structures containing a little albuminous exudate or fibrin and an occasional leucocyte or red cell. (Haematoxylin and eosin × 160.)

was free of lipoid which was confined to the reticularis and inner fasciculata This *inversion* of lipoid loss was found only in patients dying a week after injury or later and was probably due to the reaccumulation of the cortical stores of lipoid It may indicate a reversion to normal function

Total depletion.—The adrenals of burned patients are sometimes completely depleted of lipoid and terms like cortical lipoid

exhaustion" have been used to describe such glands Unfortunately, by an extension of meaning and on inadequate evidence, lipoid depletion has been equated with a physiologically exhausted or non-secretory state, but there is no evidence that such cells are inactive or exhausted On the contrary Symington and his colleagues found that they are rich in ribonucleic acid, dehydrogenase and phosphatase which indicates that they are functioning cells, they also showed that similar cytological pictures were present in glands stimulated by ACTH before removal Furthermore a close correlation was found between loss of adrenal lipoid and eosinopenia of the blood and spleen (Sevitt, 1955) Eosinopenia is regarded as a sensitive index of adrenocortical hyperactivity and therefore lipoid depletion indicates hyperactivity, even when the depletion is complete and involves the whole cortex Lipoid-depleted cortical cells are hyperactive or recently hyperactive cells

QUESTION OF ADRENOCORTICAL FAILURE

Weiskotten (1917, 1919) was impressed by the hyperaemia and focal necrosis in the adrenals of fatally burned subjects and believed that toxaemia was the cause, and various workers have claimed that glandular failure or exhaustion is not uncommon after burning and may be responsible for circulatory failure or other lethal complications Although it is now known that hyperactivity is the rule this does not exclude the occasional occurrence of adrenal failure by haemorrhage or other means Theoretically acute adrenal failure might develop either at the adrenal level or at the hypothalamic-pituitary (supra-adrenal) level corresponding to the chronic states of Addison's and Simmonds's diseases An investigation by Sevitt (1954) showed that adrenocortical hyperactivity was present in at least 49 out of 54 burned patients including a number who died but in five subjects the possibility of adrenal failure arose, in two at the adrenal level and in the others at the supra-adrenal level In the first two, normal eosinophil depression curves were not obtained by test injections of ACTH but the evidence of adrenal failure was not conclusive In the other three, ACTH tests were normal but repeated tests with adrenaline were not followed by the normal eosinopenic reaction Thus the possibility of adrenocortical failure at the hypothalamic-pituitary level arose The children were confused and irrational at the time but later, when they had mentally recovered, normal eosinopenic responses to adrenaline were obtained Similar cases have since been found It may be that both the mental disturbance and the failure to induce eosinopenia with adrenaline resulted from similar changes in the cerebral cortex and hypothalamus respectively

Hormone therapy—The clinical uses of hormones are of two main kinds, (1) those based on the physiological correction of a known endocrine deficiency such as in the treatment of Addison's disease, and (2) those based on a non specific empirical or pharmacological action of the hormone such as the cortisone therapy of rheumatoid arthritis

ACTH cortisone and other steroids—Adrenocortical extracts desoxycorticosterone acetate (DOCA) cortisone and ACTH have been used therapeutically in burned and injured patients either in the belief that they reduce the capillary exudation of fluid in the damaged area and so lessen the degree of oligaemia or that they have "non specific anti shock life saving or other beneficial properties (Wilson Rowley and Gray 1936 Elkington 1939 Scudder 1940 Crassweller and McLachlin 1950 Adams and his colleagues, 1951 Mulholland 1951 Whitelaw 1951 Olsen 1952) The evidence that these agents have no effect on capillary permeability and oedema in burned skin is outlined in Chapter 3 The clinical impression that less plasma needs to be transfused to extensively burned patients treated with these drugs than to others is probably false and arises from the wide variations in the rate and volume of plasma transfusion required for badly burned subjects The proper investigation of the possible anti-shock and life saving powers of cortisone ACTH and other agents would require a carefully controlled clinical trial involving many patients because *inter alia* the mortality after burning is variable and depends on the extent of burning, the age of the patients, pre-existing disease, other manner of treatment the incidence of infection renal failure and other complications (Chapter 8) There is experimental evidence that neither cortical extract nor DOCA have any effect on the mortality or survival of burned mice and rats (Rosenthal, 1943 Bergman and his colleagues, 1945) and the high mortality among the 22 severely burned patients treated with cortisone and ACTH by Martin McGarity and Smith (1955) indicates that these drugs have no life saving power Hence the claims of clinical efficacy mentioned above must be viewed with suspicion Indeed the clinical experiences of different workers were often inconsistent and one group altered their favourable impression after further experience (Rhoads and his colleagues 1943) Therapy with ACTH or cortisone is not without danger Infective and septicaemic complications are not uncommon after extensive burning and are difficult to prevent and control even with modern methods That such therapy might increase the frequency of these complications is suggested by the experience of Martin, McGarity and Smith (1955) Furthermore post burn

duodenal ulcers have been known to perforate in patients treated with ACTH (Mulholland, 1951) The routine use of ACTH, cortisone and other steroids is not indicated

Replacement therapy with ACTH or cortisone would be indicated if, in a particular patient there was evidence of adrenocortical failure As has already been mentioned this does not occur in at least 90 per cent of burned patients and there is no place for the routine administration of cortisone or ACTH as "replacement" therapy There may be a place for treating an occasional patient with one or other of these drugs but the clinical suspicion should be supported by haematological and biochemical evidence The following tests are recommended when it is not possible to carry out corticosteroid estimations on the blood or urine

(1) *Blood eosinophil counts and the ACTH test* (*modified Thorn test*) The blood eosinophils should be enumerated by one of the many direct "wet field" methods (such as Dunger, 1910) If eosinopenia is present (less than 40 per cubic millimetre) adrenocortical hyperactivity may be presumed, but this should be confirmed by estimating the sodium in the urine

If eosinopenia is absent an intramuscular injection of 25 milligrams ACTH (of known batch potency) should be given and the eosinophil count repeated hourly The usual procedure of making only a pre-injection count and a count 4 hours later is not recommended Normally the eosinophils commence to fall within an hour or so of injection and continues during the next 2 to 4 hours, a minimum level being reached 3–5 hours after the injection (Fig 69) In the normal response the maximum fall varies from 60 per cent to 90 per cent of the pre-injection level In assessing the significance of the result both the shape of the curve and the maximum fall should be considered A normal result indicates normal stimulable reserves of the adrenal cortex and means that cortisone is not indicated It does not eliminate supra-adrenal failure A typically abnormal response is one in which the count does not fall significantly during the period of the test Such a result might also be obtained if there was failure of absorption or a local destruction of the injected ACTH If there is doubt about the meaning of the result the test should be continued by a slow intravenous injection of 25 milligrams ACTH in saline over 8—12 hours, and the eosinophil counts repeated 4 hourly This could be combined with an estimation of the 17-ketosteroid excretion over a 24-hour period

(2) *Urinary sodium*—The 24-hour excretion should be estimated The concentration in a spot sample may serve if the value is very

low but rapid fluctuations in the excretion and concentration of sodium may make an analysis of a spot sample unreliable particularly in the early period after burning (*see* page 180) A low excretion may be taken to support adrenocortical activity if intake of salt is adequate

(3) *Adrenocortical stimulability at the hypothalamic pituitary level* — This may be tested for by giving an intramuscular injection of a *small* dose of adrenaline (0 3 milligrams) and estimating the blood eosinophils hourly for 4 hours The normal eosinopenic curve is different from that in the ACTH test (Fig. 69) Eosinopenia is maximum at about 2–3 hours after the injection and the maximum fall in the count varies from 45 per cent to 70 per cent

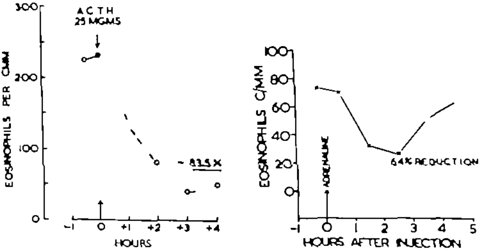


FIG 69 —Blood eosinophil responses in normal persons following injections of ACTH and adrenaline. Note that the eosinopenic response to 25 milligrams of ACTH is quicker more prolonged and generally greater than that following 0 3 milligram of adrenaline

(4) *Other tests* of some value are estimations of the blood glucose and 17 ketosteroid urinary excretion

ADRENAL MEDULLA

Hyperadrenalinaemia develops soon after burning and is responsible at least in part, for the early rise in the blood sugar and depletion of muscle glycogen (*see* Chapter 17—Carbohydrate Metabolism) and possibly for the initial increases in the blood pressure and pulse rate On the other hand adrenaline secretion is not responsible for the reduced urine flow in burned dogs (Barac, 1947) Using the pupil dilatation test direct evidence of hyperadrenalinaemia in burned cats was furnished by Hartman Rose and Smith (1926) who also claimed

that the adrenaline content of the medulla was reduced This supports the view of Cannon (1915) that fright, pain and other harmful or potentially harmful stimuli cause the release of adrenaline The relationship of adrenal medullary secretion to pituitary-adrenocortical hyperactivity has been discussed

THYROID GLAND

Thyroid activity after burning has been studied histologically, biochemically and metabolically the morphological evidence indicates hyperfunction, the biochemical studies do not support this and the metabolic evidence is conflicting The thyroid glands of patients dying within a few days of burning constantly show the nibbled marginal appearance and vacuolation of colloid suggestive of hyperexcretion (Gibson, 1945) and histological studies of experimentally burned rabbits (Rumiantsiev, 1944) and guinea-pigs (Romani, 1952) support this Rumiantsiev estimated the proportions of active and inactive tissue during the first few days and concluded that at first the thyroid is very active but by the second day after burning most of it was returning to normal After the onset of infection glandular activity was again raised Romani found an increase in height of the gland epithelium as well as vacuolation and nibbling of the colloid and thought that these indicated hypersecretion and hyperexcretion of thyroid hormone

On the other hand measurements in burned patients of the protein-bound iodine content of the serum and of the uptake of radioactive iodine by the thyroid were found to be within normal limits and did not indicate an increase of thyroid function (Cope and his colleagues, 1953)

Changes in the basal metabolic rate after burning as measured by oxygen consumption might be expected to shed some light on thyroid activity even though oxygen consumption is also determined by other influences Unfortunately there is disagreement about the changes found A decreased consumption of oxygen, 40–50 per cent below the basal rate, was reported by Henderson, Prince and Haggard (1917) a lowered consumption was also found by Cournand and his colleagues (1943) in 4 patients studied during the shock period before intravenous therapy had commenced no appreciable effect on burned rats was found by Sellers, You and You (1950), whilst an increased consumption of 30–60 per cent above the basal rate was found in patients not only during the later katabolic phase, when it might be expected, but also during the first 12 to 24 hours (Taylor, Levenson and Adams 1944, Cope and his colleagues, 1953) The conflicting

results may be related to restlessness and movement in some patients or to the absence of therapy in some and the influence of intravenous therapy and an improved circulation in others

The relationship of thyroid function to the increased loss of urinary nitrogen is discussed in Chapter 17

POSTERIOR PITUITARY

Antidiuretic hormone is released after various stimuli particularly pain (Theobald and Verney 1935) and its release might be expected after burning Using a method for the isolation of antidiuretin Baar (1956) fractionated the urine of burned patients and isolated a peptide resembling antidiuretin but found that it had little antidiuretic activity in rats

ENDOCRINOLOGICAL SEQUELAE

Amenorrhoea —This is a common occurrence in burned women and usually lasts a few months

Hirsuties —In 6 females reported by Cope and his colleagues (1943) amenorrhoea was associated with the growth of hair on the face neck and extremities but when menstruation returned the hair began to fall out They noted that the urinary 17 ketosteroid excretion was low when hirsuties developed but rose to normal when menses returned This contrasted with the raised ketosteroid excretion of women with hirsuties from other causes and they suggested that there was either an increased utilization of masculinizing hormones by the patients or a lack of balance between the secretion of adrenal androgens and ovarian hormones Excessive growth of hair also occurs in men convalescent from burns and occasionally there is a good growth of hair on a previously bald scalp (Jackson 1955)

Addison s disease —A case of Addison s disease developing about a year after burning was described by Levenson and his colleagues (1947) The adrenal hypofunction was the result of amyloid infiltration of the organ with secondary atrophy and the amyloidosis involved the spleen kidneys and other organs The amyloidosis probably resulted from a long standing infection of the unhealed burns

REFERENCES

Adams, F H., Berglund E. Balkin, S G and Chisholm, T (1951) *J Amer med Ass*., 146, 31
Baar S. (1956). *J clin Path* 9 144
Barac G (1947). *C R. Soc Biol* 141 952

that the adrenaline content of the medulla was reduced This supports the view of Cannon (1915) that fright, pain and other harmful or potentially harmful stimuli cause the release of adrenaline The relationship of adrenal medullary secretion to pituitary-adrenocortical hyperactivity has been discussed

THYROID GLAND

Thyroid activity after burning has been studied histologically, biochemically and metabolically the morphological evidence indicates hyperfunction, the biochemical studies do not support this and the metabolic evidence is conflicting The thyroid glands of patients dying within a few days of burning constantly show the nibbled marginal appearance and vacuolation of colloid suggestive of hyperexcretion (Gibson, 1945) and histological studies of experimentally burned rabbits (Rumiantsiev, 1944) and guinea-pigs (Romani, 1952) support this Rumiantsiev estimated the proportions of active and inactive tissue during the first few days and concluded that at first the thyroid is very active but by the second day after burning most of it was returning to normal After the onset of infection glandular activity was again raised Romani found an increase in height of the gland epithelium as well as vacuolation and nibbling of the colloid and thought that these indicated hypersecretion and hyperexcretion of thyroid hormone

On the other hand measurements in burned patients of the protein-bound iodine content of the serum and of the uptake of radioactive iodine by the thyroid were found to be within normal limits and did not indicate an increase of thyroid function (Cope and his colleagues, 1953)

Changes in the basal metabolic rate after burning as measured by oxygen consumption might be expected to shed some light on thyroid activity even though oxygen consumption is also determined by other influences Unfortunately there is disagreement about the changes found A decreased consumption of oxygen, 40–50 per cent below the basal rate, was reported by Henderson, Prince and Haggard (1917), a lowered consumption was also found by Cournand and his colleagues (1943) in 4 patients studied during the shock period before intravenous therapy had commenced, no appreciable effect on burned rats was found by Sellers, You and You (1950), whilst an increased consumption of 30–60 per cent above the basal rate was found in patients not only during the later katabolic phase, when it might be expected, but also during the first 12 to 24 hours (Taylor, Levenson and Adams, 1944, Cope and his colleagues, 1953) The conflicting

Pearse, A G E (1952) *J Path Bact* 64 811
Pfeiffer H (1919–20) *Z ges exp Med* 10 1
Pincus, G., Hechter O and Zaffaroni, A (1951) In *Proc Second Clin. A C T.H Conf* Ed. J R Mote New York Blakiston.
Prunty F T G (1950) *J clin Path*, 3, 87
— Forsham, P H and Thorn, G W (1948) *Clin Sci.*, 7 109
Rhoads, J E., Wolff W A Saltonstall H and Lee W E (1943) *Ann Surg.*, **118**, 982.
Rich, A. R. (1944) *Johns Hopk Hosp Bull* 74 1
Romani, J D (1952) *C R Soc Biol Paris* **146**, 1685
Rosenthal, S M (1943) *U S Pub Hlth. Rep.*, **58**, 513
Rumiantsev A. V (1944). *Biull. eksp biol med* **18**, 69
Sayers, G., and Sayers, M A. (1949) *Ann N Y Acad. Sci* **50**, 522.
Scudder J (1940) *Shock* Philadelphia Lippincott
Sellers, E A. You, S. S., and You, R. W (1950) *Endocrinology* 47 148
Sevitt, S. (1951) *Brit med. J* 1 976
— (1954) *Ibid.* 1 541
— (1955) *J Path. Bact* 70 65
Shanklin, W (1956). *Acta Endocrinol.*, **2**, 1
Singer B., and Stack Dunne, M P (1955) *J Endocrin* **12**, 130.
Speirs, R. S and Meyer R. K. (1949) *Endocrinology* **45**, 403
Sprague R. G Power M H., Mason, H. L. Albert, A., Mathieson, D R. Hench, P S Kendall E. C., Slocumb C H and Polley H F (1950) *Arch. Intern Med.*, **85**, 199
Symington T Currie A. R. Curran, R C and Davidson, J N (1955) In *Ciba Foundation Colloquia on Endocrinology* Vol. **8**, p 70 London Churchill
— and Davidson, J N (1956) *Scottish med. J*, **1**, 15
— Duguid W P and Davidson, J N (1955) Quoted by Currie and Symington (1955b)
Talbot, N B., Albright, F Saltzman, A. H. Zingmuntowicz, A. and Wixom, R. (1947) *J clin. Endocrin.* 7 331
Taylor F H L Levenson, S. M., and Adams, M A. (1944) *New Engl. J Med.* **231** 437
Theobald, G W and Verney E B (1935) *J Physiol* **83**, 341
Thorn, G W (1951) In *Symposium on Burns* p 97 National Research Council, Washington.
— Prunty, F T G and Forsham, P H (1947a) *Trans Ass Amer Phys* 60 143
— — — (1947b) *Science* **105** 528
Tompsett, S L., and Oastler E G (1947) *Glasgow med. J.*, **28**, 349
Venning, E. H., Kazmin, V E Ripstein, M McAlpine, H. T., and Hoffman M M (1948) *J clin Endocrin.* **8**, 605
Vogt, M., (1944) *J Physiol.*, **103** 317
Wardlaw H. S H. (1950). *Med. J Aust.*, **2**, 899
Weiskotten, H. G (1917) *J Amer med Ass.*, 69 776.
— (1919) *Ibid.*, 72, 259
Whitelaw M J (1951) *J Amer med. Ass.*, **145**, 85
Wilson, W C Rowley G D and Gray N A (1936) *Lancet* **2**, 1400

Bekauri, N V, Danilov, A A, and Moissejeff, E A (1944) *C R Acad Sci U S S R*, 42, 238
Bergman, H C, Rosenfield, A B, Hechter, O, and Prinzmetal, M (1945) *Amer Heart J*, 29, 506
Browne, J S L (1951) In *Symposium on Burns*, p 102 National Research Council, Washington
Cannon, W B (1915) *Bodily Changes in Pain, Hunger, Fear and Rage* New York, Appleton
Chorvat, J (1955) *S C R Soviet med Bull*, 2, 17
Clark, E J, and Rossiter, R J (1944) *Quart J exp Physiol*, 32, 279
Conn, J W, Louis, L H, and Johnson, M W (1949) *J Lab clin Med*, 34, 255
Cope, O, Nathanson, I T, Rourke, G H, and Wilson, H (1943) *Ann Surg*, **117**, 937
— Naidi, G L, Quijano, M, Rovit, R L, Stanbury, J B, and Wight, A (1953) *Ibid*, **137**, 165
Cournand, A, Riley, R L, Bradley, S E, Breed, E S, Noble, R P, Lauson, H D, Gregerson, M I, and Richards, D W (1943) *Surgery*, **13**, 964
Crassweller, P O, and McLachlin, A D (1950) *Brit med J*, **2**, 977
Crema, C (1928) *Boll Soc ital biol sper*, **3**, 59
Currie, A R, and Symington, T (1955a) In *Ciba Foundation Colloquia on Endocrinology*, Vol **8**, p 396 London, Churchill
— — (1955b) *Proc R Soc Med*, **48**, 908
Delarue, J, Monsaingeon, A, and Laumonier, R (1950) *Pr Med*, **82**, 1446
Dixon, H B F (1955) *Proc R Soc Med*, **48**, 903
Dougherty, T F, and White, A (1947) *J Lab clin Med*, **32**, 584
Dunger, R (1910) *Munch med Wschr*, **57**, 1942
Elkington, J R (1939) *Bull Ayer clin Lab*, **3**, 279
Evans, E I, and Butterfield, W J H (1951) *Ann Surg*, **134**, 588
Finerty, J C, Hess, M, and Binhammer, R (1952) *Anat Rec*, **114**, 115
Forsham, P H, Thorn, G W, Prunty, F T G, and Hills, A G (1948) *J clin Endocrin*, **8**, 15
Fulton, J F (1948) *Functional Localization in the Frontal Lobes and Cerebellum* Oxford, Clarendon Press
Gibson, T (1945) In *Studies of Burns and Scalds*, p 196 M R C Special Report Series No 249
de Groot, J, and Harris, G W (1950) *J Physiol*, **111**, 335
Harkins, H N, and Long, C N H (1945) *Amer J Physiol*, **144**, 661
Harris, R I (1929) *Brit J Surg*, **16**, 677
Hartman, F A, Rose, W J, and Smith, E P (1926) *Amer J Physiol*, **78**, 47
Heard, R D H, Sobel, H, and Venning, E H (1946) *J Biol Chem*, **165** 699
Henderson, Y, Prince, A L, and Haggard, H W (1917) *J Amer med Ass*, **69**, 965
Hills, A G, Forsham, P H, and Finch, C A (1948) *Blood*, **3**, 755
Hume, D M, and Wittenstein, G J (1950) In *Proc First Clin A C T H Conf* Ed J R Mote Philadelphia, Blakiston
— Nelson, D N, and Miller, D W (1956) *U S Naval Med Res Inst*, **14**, 87
Jackson, D McG (1955) Personal communication
Levenson, S M, Tagnon, H J, Goodpastor, W L, Green, W R, Taylor, F H L, and Lund, C C (1947) *New Engl J Med*, **237**, 152
Long, C N H (1947) In *Recent Progr Hormone Res*, **1**, 99
— and Fry, E G (1945) *Proc Soc exp Biol, N Y*, **59**, 67
— Katzin, B, and Fry, E G (1940) *Endocrinology*, **26**, 309
McDermott, W V, Fry, E G, Brobeck, J R, and Long, C N H (1950) *Proc Soc exp Biol, N Y*, **59**, 67
Marshall, J M (1951) *J exp Med*, **94**, 21
Martin, J D, McGarity, W C, and Smith, F C (1955) *Surgery*, **38**, 543
Mulholland, J (1951) *Ann Surg*, **134**, 636
Nakata, T (1925) *Beitr Path Anat*, **73**, 439
Olsen, A (1952) *Acta endocrinol*, **9**, 1

occur In mining explosions the victims are surrounded by a flash of flame and may subsequently breathe air and fumes at a high temperature

The injurious effects of fire and smoke in conflagrations may be caused by (1) anoxia due to suffocation (2) the inhalation of carbon monoxide, (3) the inhalation of irritant gases and fumes, and (4) burns of the airway particularly the larynx These may occur singly or in combination

Carbon monoxide poisoning—Carboxy haemoglobinaemia from the inhalation of carbon monoxide may occur when a fire breaks out in a confined space or in a building causing incomplete combustion In the author s experience patients admitted to hospital may have small or extensive burns and the carboxy haemoglobin content of the blood may be up to 30 per cent or even 50 per cent Asphyxia from carbon monoxide poisoning may cause or contribute to death during the subsequent few days, or sometimes the patients die soon after burning. For example Mallory and Brickley (1943) reported 3 burned patients who were brought in dead to hospital after the fire in the Coconut Grove nightclub in the U S A They had a carboxy haemoglobin content of 42–50 per cent in the blood as well as a haemorrhagic laryngo-tracheo-bronchitis and pulmonary oedema

Inhalation of irritant gases and smokes.—It is well known that the inhalation of various gases, fumes and smokes produced by combustion is injurious to the respiratory tract—witness the respiratory deaths from the smoke fog mixture (smog) in London Los Angeles and elsewhere. *A priori* the breathing of these irritants in higher concentration such as is likely to be found in a conflagration should lead to a severe irritation of the respiratory mucous membrane However it may be difficult to evaluate the effects of respiratory irritants and to distinguish them from those following the inhalation of hot air or flame Moreover the chemical and physical nature of the fumes and smoke vary from fire to fire Some kinds are more toxic than others and although sulphurous and nitrous fumes are known to be particularly dangerous more information is required about the relative injurious effects of particulate carbon, methane other hydrocarbons and other products of combustion

After the Coconut Grove disaster most of the patients had acute respiratory symptoms which were often severe, but in a few patients respiratory symptoms were absent (Aub Pittman and Brues 1943 Finland Davidson and Levenson 1946a Finland 1951) These patients were reported to have covered their mouths with wet cloths suggesting that the inhalation of flame or very hot air had

CHAPTER 19

RESPIRATORY TRACT

DISORDERS of respiration and changes in the respiratory tract are not uncommon in burned patients Sometimes they obviously arise from the inhalation of hot air or various fumes, smokes and gases or from both causes, but other patients often develop polypnoea or respiratory distress The clinical and pathological pictures are unclear, firstly because the effects of inhalation of hot air on the one hand and various fumes and smokes on the other are often confused, and secondly because the cause or causes of polypnoea, respiratory distress or respiratory failure are often unknown There is evidence that congestive atelectasis and perhaps pulmonary oedema play some part in the respiratory embarrassment of some patients but a close correlation between symptomatology and morbid anatomical changes has not been established There may be evidence of a deficient oxygenation of the blood passing through the lungs since Richards (1943–44) found that the oxygen saturation of the arterial blood was often reduced He investigated 19 patients in 12 of whom the saturation was reduced to between 81 per cent and 89 per cent for 3–7 days In some cases inhalation of hot or irritant gases may have been responsible but in others there was no obvious cause The reduced oxygenation suggests that oxygen therapy may be helpful in some patients

Lack of essential knowledge produces a difficulty in classification and for want of a better one disorders of respiration and of the respiratory tract are classified into (1) burns of the respiratory tract including the inhalation of noxious and irritant smokes and gases, and (2) other forms of respiratory distress, often associated with congestive atelectasis and pulmonary oedema In addition complications such as pneumonia and pulmonary embolism may occur

RESPIRATORY BURNS AND THE INHALATION OF GASES AND SMOKES

Respiratory complications are particularly important in fires which spread rapidly in buildings and ships and also in mines, aircraft, tanks and other confined spaces In such circumstances hot air, flame, carbon monoxide and irritant gases and smokes are liable to be inhaled, and respiratory lesions with or without skin burns may

Accidental burns to the airway.—These usually result from the inhalation of flame or hot air and occasionally from steam or hot liquid. The major effect is laryngeal oedema due to a direct thermal injury of the laryngeal mucous membrane. This is often associated with flame burns of the face and of the upper part of the chest. A common set of circumstances is that the victim's clothes catch fire, there is a delay before the flames are extinguished and the patient inhales flame and hot air. Inhalation of steam or hot fluid is said to produce particularly severe burns.

The patient may die of asphyxia from obstructive laryngeal oedema shortly after the accident, but in most cases symptoms of respiratory distress are delayed for hours. Cough, laboured breathing and perhaps stridor develop and cyanosis may occur. Respiratory obstruction from oedema of the glottis should be relieved by tracheotomy. Bronchial stridor may develop, moist sounds may be heard in the lungs and there may be clinical or radiological evidence of pulmonary collapse or oedema. In mild cases symptoms consist of cough, hoarseness and a painful throat. Symptoms of acute respiratory distress (except perhaps laryngeal stridor) are not infrequent but are not diagnostic of either respiratory burns or the inhalation of irritants because similar symptoms may occur in extensively burned patients who show no evidence of laryngeal oedema or other damage to the respiratory mucous membrane at autopsy.

Necropsy findings.—Although the face and lips may be burned and oedematous the mucosa of the nose, mouth and palate may escape serious injury. The changes found at autopsy may result either from thermal injury or the inhalation of irritant smokes and fumes or from both causes, but some of the findings in the lungs might result from anoxia or the indirect effects of extensive burning (*vide infra*). The abnormal findings are (1) oedema of the larynx, (2) a laryngo-tracheo-bronchitis which is sometimes membranous and (3) pulmonary changes, particularly congestion, emphysema, atelectasis and oedema.

Oedema of the larynx.—This is the main effect of *thermal* injury. The oedema particularly affects the aryteno-epiglottic folds and the pyriform fossae of the pharynx but it may also extend around and above the vocal cords.

Membranous laryngo-tracheo-bronchitis.—Inflammation of the airway may be haemorrhagic but in the severest cases it is ulcero-necrotic and a pseudo-diphtheritic false membrane forms. This is composed of fibrin, necrotic mucosa and leucocytes and is rapidly

produced the respiratory lesions in the others On the other hand the sputa of those with respiratory symptoms were blackened with carbon, which indicated that considerable smoke had been inhaled and that therefore the wet cloth may have acted as a filter in the others Finland (1951) concluded that the respiratory injuries were the combined result of flames, hot air, hot particles and various noxious gases produced by combustion, but the experiments reported by Moritz (1951) indicated that nitrous fumes may have been responsible When he burned leatherette decorations from the nightclub, toxic oxides of nitrogen were formed and the fumes were poisonous to experimental animals

Experimental burns of the airway—It is often assumed that when the skin is not burned respiratory damage results from the inhalation of smoke and other irritants, whilst if skin burns are present the respiratory damage is due to heat The experimental work of Moritz and his colleagues indicates that the major effect of inhaling hot air or flame is on the upper airway, and that if the hot air is potentially capable of injuring the lungs it rapidly causes a fatal oedema of the larynx before it can do so (Moritz, 1945, Moritz, Henriques and McLean, 1945, Moritz, 1951) When a blast of air at 500°C was delivered to the laryngo-pharynx of dogs the animals died a few hours later from glottic oedema During burning the air temperature was between 260° and 280°C in the larynx but it fell to below 50°C in the trachea The mucous membrane of the upper trachea was damaged but there was no evidence of pulmonary injury When air heated to 300–350°C was inhaled through a transoral cannula projecting beyond the vocal cords there was no clinical evidence of respiratory damage and only the upper trachea showed a catarrhal inflammation Thus air hot enough to burn the skin was inhaled without damage to the lower trachea or lungs Even when flame was inhaled through the cannula most of the animals showed no evidence of pulmonary injury although the upper trachea was severely damaged On the other hand inhalation of steam was usually followed by severe bronchial and pulmonary injury the tracheo-bronchial mucosa became necrotic and there was a diffuse haemorrhagic oedema in the central parts of the lungs

The different effects of dry heat and steam depend on the very low heat capacity of air and the high latent heat of steam Hot dry air cools rapidly when it enters the air passages, producing its major effect on the larynx and little or no changes in the bronchi or lungs, whilst steam affects the whole length of the airway and damages the lungs because its latent heat is released when it changes to water

Accidental burns to the airway.—These usually result from the inhalation of flame or hot air and occasionally from steam or hot liquid. The major effect is laryngeal oedema due to a direct thermal injury of the laryngeal mucous membrane. This is often associated with flame burns of the face and of the upper part of the chest. A common set of circumstances is that the victim's clothes catch fire, there is a delay before the flames are extinguished and the patient inhales flame and hot air. Inhalation of steam or hot fluid is said to produce particularly severe burns.

The patient may die of asphyxia from obstructive laryngeal oedema shortly after the accident but in most cases symptoms of respiratory distress are delayed for hours. Cough, laboured breathing and perhaps stridor develop and cyanosis may occur. Respiratory obstruction from oedema of the glottis should be relieved by tracheotomy. Bronchial stridor may develop, moist sounds may be heard in the lungs and there may be clinical or radiological evidence of pulmonary collapse or oedema. In mild cases symptoms consist of cough, hoarseness and a painful throat. Symptoms of acute respiratory distress (except perhaps laryngeal stridor) are not infrequent but are not diagnostic of either respiratory burns or the inhalation of irritants because similar symptoms may occur in extensively burned patients who show no evidence of laryngeal oedema or other damage to the respiratory mucous membrane at autopsy.

Necropsy findings.—Although the face and lips may be burned and oedematous the mucosa of the nose, mouth and palate may escape serious injury. The changes found at autopsy may result either from thermal injury or the inhalation of irritant smokes and fumes or from both causes but some of the findings in the lungs might result from anoxia or the indirect effects of extensive burning (*vide infra*). The abnormal findings are (1) oedema of the larynx, (2) a laryngo-tracheo-bronchitis which is sometimes membranous and (3) pulmonary changes, particularly congestion, emphysema, atelectasis and oedema.

Oedema of the larynx.—This is the main effect of *thermal* injury. The oedema particularly affects the aryteno-epiglottic folds and the pyriform fossae of the pharynx but it may also extend around and above the vocal cords.

Membranous laryngo-tracheo-bronchitis.—Inflammation of the airway may be haemorrhagic but in the severest cases it is ulcero-necrotic and a pseudo-diphtheritic false membrane forms. This is composed of fibrin, necrotic mucosa and leucocytes and is rapidly

invaded by various bacteria, it is whitish or grey or may be mixed with a sanguinous exudate The membrane is usually easily removed from the interior of the airway but it may be adherent in places The trachea is usually affected and sometimes the larynx below the vocal cords, whilst occasionally the membrane extends into the main bronchi and even into the secondary, tertiary and further divisions within the lungs Cases of this kind were described by Mallory and Brickley (1943) and Finland, Davidson and Levenson (1946a) and were probably due to inhalation of irritant fumes rather than to heat (*vide supra*) Mallory and Brickley found that plugging of bronchi could follow separation and coiling of the false membrane and that small blisters were sometimes formed in the small bronchi

Pulmonary lesions —These vary considerably from patient to patient Acute congestion is invariable, acute emphysema, a patchy or lobar atelectasis, areas of intra-alveolar haemorrhage (some resembling infarcts) and oedema may all occur in the same patient and in the same lung, although sometimes one is more prominent than the others The finding of well aerated, distended and acutely emphysematous lungs sometimes with subpleural bullae is indicative of expiratory obstruction However the other lesions are also frequently found in other patients dying within a few days of burning and may not result from inhalation of irritants Mallory and Brickley described multiple small thrombi in the pulmonary vessels which they considered responsible for the lobular infarct-like haemorrhagic areas present

Pulmonary oedema and plasma transfusion.—In oedema of the lungs the permeability of the alveolar capillaries is increased and permits the passage of a protein-rich exudate into the alveoli from the blood stream Exudation into the lungs would increase the plasma oligaemia of extensively burned patients during the shock phase and as a consequence more plasma would need to be transfused to maintain the plasma volume In such patients continued transfusion may increase the volume of the intra-pulmonary exudate and the patient may drown in the excess The paradox of therapy in burned patients with a leaking pulmonary circulation is whether to reduce the rate of transfusion and risk circulatory and renal failure or to transfuse "adequately" and risk death from pulmonary oedema The management of burn shock complicated by pulmonary damage was discussed by Cope and Rhinelander (1943) who reported that the plasma requirements of the patients were considerably increased and that the increased transfusion aggravated the danger of fatal pulmonary oedema On the other hand Finland, Davidson and Levenson

(1946b) and Finland (1951) reported that the large amounts of plasma used in patients with severe respiratory symptoms were necessary because the surface burns were extensive and they considered that the pulmonary complications were probably not aggravated by the large volumes administered It has already been noted that severe respiratory symptoms and pulmonary lesions may or may not be associated with pulmonary oedema and it is possible that the absence of significant oedema may have accounted for Finland s experience

The clinical relevance is that respiratory distress is not necessarily equated with pulmonary oedema and a firm diagnosis of the latter should be made before deciding to change the rate of plasma transfusion

OTHER FORMS OF RESPIRATORY DISTRESS

It is not generally recognized that acute respiratory symptoms are common in extensively burned patients, particularly in children and that sometimes distress occurs This change is distinct from the symptoms which may follow inhalation of flame, hot air and irritating smokes The respiratory rate may increase considerably (rates of 40–60 per minute are common) at any time during the first few days and the polypnoea is commonly accompanied by pyrexia and tachycardia and sometimes by mental disturbance. Neither the polypnoea nor the pyrexia appear to be influenced by intravenous transfusion The patient may be a little cyanosed but this is not prominent, and clinically the condition may resemble acute bronchopneumonia Examination of the chest may reveal scattered areas of dullness bronchial breath sounds and some moist râles but physical signs may be absent Some patients die within a few days in respiratory distress and the symptoms may continue for two or three weeks in others Gibson (1945) described three children who died in respiratory distress 4 days after burning, and noted that respiratory symptoms were common in other burned children At autopsy he found a patchy collapse of the lungs and some congestion of the bronchial mucosa.

Wilson Macgregor and Stewart (1938) noted that lesions of the respiratory tract were often associated with burns of the chest and thought that this indicated inhalation of hot air Extensive severe burns of the chest wall which render the skin tough leathery and brown may also interfere with thoracic movement and in such cases incision of the burned skin or primary excision of the area may be of some value in relieving distress The bronchial secretions often increase and may necessitate tracheo-bronchial suction Neither of these measures cure the distress although they may temporarily alleviate symptoms Bronchopneumonia may supervene

Acute respiratory failure.—Sudden cessation of breathing, apparently the result of cerebral changes, has been reported Walker and Shenkin (1945) described a group of patients dying in acute respiratory failure 3–5 days after burning At autopsy there was evidence of a raised intracranial pressure sometimes with tentorial or medullary-cerebellar pressure coning and histological evidence of ganglion-cell degeneration, particularly in the hypothalamus

Necropsy findings.—Patients who die during the first few days after burning regularly have congested lungs and the pleurae frequently show petechial haemorrhages (Pack, 1926, Erb, Morgan and Farmer, 1943), with this may be associated a variable degree of atelectasis and pulmonary oedema Gibson (1945) found that collapse of the lungs was not infrequent in patients dying during the shock period, and Erb, Morgan and Farmer (1943) noted that the degree of congestion and oedema increased during the first three days, after which it was commonly complicated by pneumonia

Congestive atelectasis and oedema —Occasionally a total or massive collapse of the lungs is found, particularly in children who die with acute respiratory symptoms (Fig 70) Sometimes pulmonary oedema is gross and bilateral and atelectasis is slight or absent Between the two extremes of massive collapse and gross oedema are the majority of cases which show a variable degree of both conditions Atelectasis may involve the upper and lower parts of the lungs but is usually more prominent in the lower lobes, while not infrequently a complete or incomplete collapse of one or both lower lobes is found The collapsed areas are more prominent in the periphery of the lung and are easily distinguished from the surrounding tissue They are purple and fleshy and have lost their air crepitus, the cut surface is often moist and may exude some blood-stained fluid In the uncollapsed areas of oedema the fluid may be frothy or free of air bubbles, the bronchial mucosa is congested and swollen and mucus may or may not be present

Histologically the alveolar capillaries are distended with erythrocytes In the collapsed areas most of the alveolar walls are approximated and many of the bronchioles may also be collapsed In other parts of the same section the alveoli may be oedematous containing an eosinophilic serous exudate and perhaps numbers of erythrocytes Sometimes intra-alveolar haemorrhage is prominent in places

Pathogenesis —The causation of polypnoea and pulmonary congestive atelectasis and oedema of the lungs requires consideration

Polypnoea.—The cause is obscure. Pathological changes in the lungs may be responsible but it should not be assumed that the changes which originate the polypnoea are the same as those which are found at autopsy. There is evidence that the rapid shallow breathing which accompanies various lung conditions including pulmonary embolism, congestion and oedema and probably pneumonia has a reflex origin. Dunn (1920) showed experimentally that a shower of starch emboli in the pulmonary arterioles was succeeded by rapid shallow breathing, but if the vagus nerves were sectioned there was no change in the respiratory rate. This and subsequent work suggests that the change in the respiratory rate originates within the lungs from proprioceptive

FIG. 70.—Massive collapse (congestive atelectasis) of both lungs causing death 24 hours after burning. Girl of 4 years with burns on 60 per cent of the body surface.

impulses passing through the vagus. Churchill and Cope (1929) showed that when one pulmonary artery was tied and the lung was isolated from the pulmonary but not from the bronchial circulation an acute rise in pulmonary arterial pressure was followed by rapid shallow breathing which soon became associated with pulmonary congestion and oedema, whilst Jenkins and his colleagues (1950) reported that the polypnoea associated with experimental pulmonary congestion was abolished by blocking the vagus nerves. The polypnoea in burned patients may therefore be reflexly produced and dependent on afferent impulses arising within the lung or its vessels. It may be that the congestion of the lungs which follows burning sometimes initiates polypnoea and that oedema and atelectasis may develop later when breathing becomes laboured. Another possibility is that the polypnoea

is of cerebral origin and that it results from a reduction in the cerebral blood flow associated with oligaemia and a reduced cardiac output when the blood pressure falls (Chapter 9) Stone and his colleagues (1954) removed 1 5–2 2 litres of blood from human volunteers and found a reduced cerebral blood flow, mental symptoms and hyperventilation In burned patients a reduced cerebral flow is unlikely to originate the changes because plasma transfusion has little or no effect, but this does not mean that cerebral changes may not be responsible

Congestion and congestive atelectasis —Oligaemia may be responsible for the initiation of pulmonary congestion because Jenkins and his colleagues (1950) found by an *in vivo* radioactive method that the pulmonary blood volume in dogs increased considerably following acute haemorrhage

Minor and moderate degrees of congestive atelectasis may be found in subjects with and without previous respiratory symptoms, but major and particularly bilateral lobar or total atelectasis is always associated with previous respiratory distress Congestive atelectasis, including the better known condition of massive pulmonary collapse, is to be distinguished from atelectasis following bronchial obstruction with which it is often confused It may be found in a variety of clinical states including post-operative collapse (Scott, 1925), head injuries (Cairns and his colleagues, 1947), after intravenous transfusion (Jenkins and his colleagues, 1950), experimental decompression (Fegler and Bannister, 1944), traumatic shock, chest and abdominal injuries and other conditions Its origin is obscure It is not due to a sticky secretion in the bronchi, although this may complicate it, and theories, such as that it is secondary to nervous or cardiovascular changes, are at present purely speculative

Pulmonary oedema —The significance of oedema is often obscure It is found more often at necropsy than diagnosed during life so that sometimes it must be a terminal event It might also arise through early circulatory embarrassment, overtransfusion, transfusion of fluid deficient in colloid or it may be neurogenic in origin (*see* Cameron, 1948)

BRONCHOPNEUMONIA

This is one of the commonest complications and causes of death in extensively burned patients who survive the first few days, and particularly in those who die weeks after burning with an extensive area of unhealed granulating skin At autopsy it is frequently associated with

a variable degree of pulmonary oedema and atelectasis Bacteriologically the pneumonia often differs from that in unburned patients in that pneumococci and *Haemophilus influenzae* in the sputum or lung are few or absent. At autopsy the lung flora is often mixed and organisms similar to those found on the burned surface are usually isolated this indicates a close relationship between the pneumonia and the infected burn In Birmingham the bacteria usually isolated are *Pseudomonas pyocyanea Staphylococcus aureus Proteus* various coliform bacilli viridans and non haemolytic streptococci or a mixture of these bacteria. Fibrinous pleurisy or empyema occasionally occur

The pneumonic state is occasionally embolic and may be associated with a number of small lung abscesses and other evidence of pyaemia

PULMONARY EMBOLISM AND DEEP VEIN THROMBOSIS

Pulmonary embolism.—Pulmonary emboli originate as thrombi in the deep veins of the lower limbs or pelvis Part of the thrombus becomes detached and carried towards the lungs

At necropsy pulmonary embolism and/or infarction was found by the author in 8 out of 108 burned patients and in 4 subjects it was the major or immediate cause of death The survival periods of the eight varied from 6 days to 2½ months 5 were elderly 2 were younger adults and 1 was a boy of 6 years One elderly woman died rapidly after a large thrombo-embolus had entered the bifurcation of the pulmonary artery in another the right main artery was blocked and there was early infarction of the lung two others showed multiple narrower emboli and numbers of infarcts In the remainder a single infarct was present Four had been extensively burned (25–65 per cent of the body surface) and the others had relatively small burns (2–5 per cent)

The over all incidence of pulmonary embolism is therefore significant but not high but this is because the majority of burned patients are children in whom venous thrombosis is uncommon and because most of the deaths in the elderly occur within a few days of burning, that is, before venous thrombosis generally develops The condition should become more frequent if more middle-aged and elderly patients were to survive a week or longer after burning Moore (1943) found radiological evidence of infarction in 2 out of 9 burned adults hospitalized for prolonged periods

Venous thrombosis.—Thrombosis of the deep veins of the lower limbs and pelvis is much more common than pulmonary embolism and is often undiagnosed It is frequent in middle aged or elderly

subjects who remain in bed for more than a few days The cause is unknown but age, immobilization, venous stasis, injury and operation are the main predisposing factors

Pathology—The veins themselves are normal The thrombi may be divided into *primary* or platelet (pale) thrombi and *secondary* or red thrombi Routine dissection of the veins of burned and injured patients at necropsy has shown that the main primary sites of

FIG 71—Thrombosis of the inferior vena cava, iliac and femoral veins in a boy of 18 months who died 1 month after burning Burns involved 25 per cent of the body area

thrombosis are (1) in the common femoral vein just below the inguinal ligament, (2) or at its junction with the deep femoral vein or other large tributaries, (3) in the external iliac vein just above the inguinal ligament, (4) in the popliteal vein near its origin, (5) in the posterior tibial veins and (6) in the deep intramuscular tributaries of the calf Forward and distal extension occur forward extension (the growing "serpent's head") is largely through deposition of platelets on the tip of the primary thrombus and it occurs more rapidly after the vein has been blocked A thrombus in the common femoral vein

may grow along the iliac veins into the inferior vena cava where it occasionally extends up to the kidneys (Fig 71) Blockage of the orifice of the opposite iliac vein is followed by secondary thrombosis of that vessel Distal extension is frequent and takes place when the vein becomes blocked by the primary thrombus Rapid fibrin clotting of the column of blood takes place as far distally as the aperture of the nearest main tributary or nearest valve and oedema of the leg or limb rapidly follows

REFERENCES

Aub J C., Pittman, H., and Brues, A. M (1943) *Ann. Surg.*, 117 834

Cairns, H. Calvert, C. A., Daniel P and Northcroft, G B (1947) *Brit J Surg War Surg Suppl.*, 1 198

Cameron, G R. (1948) *Brit med J.*, 1 965

Churchill, E. D and Cope, O (1929) *J exp Med.*, 49 531

Cope, O and Rhinelander F W (1943). *Ann Surg* 117 915

Dunn, J S (1920) *Quart J Med* 13 129

Erb, I H. Morgan E. M and Farmer A. W (1943) *Ann. Surg* 117 234

Fegler J., and Bannister J (1944) *Quart J exp Physiol* 33, 291

Finland, M (1951) In *Symposium on Burns* p 91 National Research Council Washington.

— Davidson, C. S., and Levenson, S M. (1946a) *Medicine Balt.*, 25 215

— — — (1946b) *Arch. Intern. Med.* 77 477

Gibson, T (1945). In *Studies of Burns and Scalds* p 192 M R.C Special Report Series No 249

Jenkins, M T Jones, R. F., Wilson, B., and Moyer C. A. (1950) *Ann Surg* 132, 327

Mallory T B., and Brickley W J (1943) *Ann Surg* 117 865

Moore, F D (1943) *Ann Surg* 117 931

Moritz, A. R. (1945). *Bull New Engl med. Cent* 7 222.

— (1951) In *Symposium on Burns* pp 86, 96. National Research Council Washington

— Henriques, F C and McLean, R. (1945) *Amer J Path.* 21 311

Pack, G T (1926) *Arch. Path. (Lab Med)* 1 767

Richards, D W (1943–44) *Harvey Lectures* 217

Scott, W J M (1925). *Arch. Surg* 10 73

Stone, H H., Mackrell, T N Brandstater B J Haidak, G L. and Nemir P (1954) *Surg Forum* 5, 789

Walker J and Shenkin, H. (1945) *Ann. Surg* 121 301

Wilson, W C Macgregor A. R. and Stewart, C. P (1938) *Brit J Surg.*, 25, 826.

subjects who remain in bed for more than a few days The cause is unknown but age, immobilization, venous stasis injury and operation are the main predisposing factors

Pathology The veins themselves are normal The thrombi may be divided into *primary* or platelet (pale) thrombi and *secondary* or red thrombi Routine dissection of the veins of burned and injured patients at necropsy has shown that the main primary sites of

FIG 71 —Thrombosis of the inferior vena cava, iliac and femoral veins in a boy of 18 months who died 1 month after burning Burns involved 25 per cent of the body area

thrombosis are (1) in the common femoral vein just below the inguinal ligament, (2) or at its junction with the deep femoral vein or other large tributaries, (3) in the external iliac vein just above the inguinal ligament, (4) in the popliteal vein near its origin, (5) in the posterior tibial veins and (6) in the deep intramuscular tributaries of the calf Forward and distal extension occur forward extension (the growing "serpent's head") is largely through deposition of platelets on the tip of the primary thrombus and it occurs more rapidly after the vein has been blocked A thrombus in the common femoral vein

spasms, choreo-athetoid movements and occasionally generalized epileptiform convulsions These symptoms are often accompanied by pyrexia an increased respiratory rate vomiting and signs of peripheral circulatory failure Episodes of hyperpyrexia are not infrequent and the body temperature may reach 103 –107°F The mental symptoms usually last 2 or 3 days but occasionally persist for a week or longer when they may be difficult to distinguish from toxic delirium and confusion

Restlessness delirium disorientation and motor symptoms may also develop in adults but are less frequent and less severe

Morphine—It is now recognized that morphine and other opiates given intramuscularly or subcutaneously as a first aid measure to burned or injured patients may have no effect at first because the poor peripheral circulation retards absorption of the drug. Rapid absorption will take place later when the circulation is restored by transfusion and the delayed effects of the drug may produce unexpected symptoms or mask the patient s clinical course For this reason morphine if indicated, should be given intravenously Elman (1944) found that morphine considerably increased the 24-hour mortality rate of severely burned dogs but this unfavourable result has been contested Rosenthal and Tabor (1945) found that in analgesic doses morphine had no adverse effect on the mortality rate of extensively burned mice

Necropsy findings.—In many of those who die during the first few days there is evidence of a raised intracranial pressure (Riehl, 1931 Walker and Shenkin 1945 Gibson 1945 Morrison 1947) The dura is stretched and under tension and the cerebral convolutions are flattened sometimes there is a pressure coning of the cerebellar tonsils around the medulla oblongata and occasionally a coning of the uncus at the free margin of the tentorium cerebelli

The brain and the pia arachnoid are congested The grey matter is often pink in colour in contrast to the white matter in which vascular puncta are prominent petechiae are not infrequent, the brain substance is softer than normal and the cut surface is often moist In untreated burned dogs dying within 12 hours of burning Keeley Gibson and Pijoan (1939) reported histological evidence of a diffuse circulatory disturbance which they attributed to anoxia The entire vascular bed was congested and there were multiple tiny scattered perivascular haemorrhages in the base of the cerebral hemispheres, thalamus corpus callosum, around the Sylvian aqueduct and in the white matter of the cerebellum

Some workers report damage to neurones and other nerve cells

CHAPTER 20

THE NERVOUS SYSTEM

THE influence of nervous activity on burn shock, on changes in the burned skin and on the reactions of various body systems and organs is discussed in other chapters, this chapter is concerned with the effects of burning on the nervous system Knowledge of these changes is meagre but cerebral changes are known to occur during burn shock and have received some attention by clinicians and pathologists Other cerebral mental and, psychological complications have been described, in some of which there is an anatomical lesion, but clinico-pathological correlation is fraught with difficulty

The cerebral effects may be classified into (1) those related to shock, (2) special complications, such as meningitis encephalitis and encephalopathy (3) psychological and allied changes In addition the brain may be affected directly by heat from burns of the cranium, and cerebral changes are often produced as uraemic manifestations of renal failure (Chapter 14) Nothing is known about changes in the spinal cord or autonomic nervous system and very little about peripheral nerves An experimental study has been reported on the changes in intramuscular nerves and motor end-plates

CEREBRAL EFFECTS OF SHOCK

The cerebral effects during the shock period may dominate the clinical picture, particularly in children, so much so is this at times that Riehl (1931) and Gibson (1945) thought that severely burned patients died a cerebral death, the patient passing through a phase of increasing mental upset to coma and death After the initial period of fright most children become quiet and co-operative and they remain like this *if colloid therapy is adequate* If therapy is delayed or inadequate the child becomes restless and his mental state alters At first he may shout and struggle but later drowsiness develops During this phase he can be roused at first and is rational but later he becomes irrational, disorientated and confused Periods of coma develop and may alternate with lucid intervals, after which coma may deepen and death supervene

Motor symptoms are not uncommon They include sudden screaming attacks, localized twitchings of the mouth or limbs, carpo-pedal

removal of 1 5–2 2 litres of blood from professional volunteers produced considerable hypotension and mental changes, such as restlessness, excitement and confusion The cerebral blood flow was found to be decreased in spite of a reduced cerebral vascular resistance, and the arterio-venous oxygen content difference of the blood to and from the head was increased

Raised intracranial pressure —The necropsy findings frequently suggest a raised intracranial pressure but reports of cerebrospinal fluid pressures in burned patients are few The observations of Gibson (1945) and Morrison (1947) indicate that the pressure is raised in patients with acute cerebral symptoms during the resuscitation period Lumbar punctures performed on three patients by Gibson and on two by Morrison all showed high intraspinal pressures (250–360 millimetres of cerebrospinal fluid) and removal of 10 millilitres of cerebrospinal fluid from one of Morrison s patients had a temporary beneficial effect.

There may be a relationship between raised intracranial tension and acute vascular hypertension because all the mentally disturbed children described by Morrison developed hypertension during the resuscitation period Vascular hypertension also occurred without mental disturbance

Cerebral oedema —A number of workers have concluded that the raised intracranial pressure and the pressure effects on the brain seen at necropsy are due to cerebral oedema (Riehl 1931 Walker and Shenkin, 1945 Morrison 1947) and it has already been noted that when the brain is sliced the cut surface often appears excessively wet Although the oedema is said to result from anoxia due to circulatory changes it is doubtful whether anoxia alone ever produces oedema of the brain or any tissue Furthermore the diagnosis at necropsy of generalized oedema of the brain is fraught with difficulty and doubt has been expressed whether the condition ever occurs Alternatively cerebral swelling due to hyperaemia and congestion of the brain could be responsible for the increase in pressure Walker and Shenkin (1945) thought that the perivascular and perineuronal spaces seen histologically meant oedema but these changes are notoriously difficult to interpret in necropsy material particularly when the tissue has been processed to paraffin wax In an attempt to settle the problem the water and chloride content in the cerebral white matter of three subjects included in Gibson s (1945) report were analysed by Anderson and Semeonoff (1945) The water content was found to be normal (68–74 per cent) and the chloride values (188–200 milligrams per 100 millilitres) were only slightly raised

Walker and Shenkin (1945) found that the brains of patients dying of acute respiratory failure showed chromatolysis of ganglion cells, cell degeneration and even death and lysis of neurones These changes, which may be secondary to anoxia, were found in different parts of the brain but were most striking in the hypothalamus In two patients dying in acute respiratory distress following inhalation of hot air and fumes, Mallory and Brickley (1943) described degeneration of many large neurones which were often surrounded by increased numbers of satellite cells, in addition the Purkinje cells were shrunken, the oligodendroglial cells were swollen and increased in number and changes in other glial cells were found Many of the changes described by Walker and Shenkin and by Mallory and Brickley might be attributed to anoxia from respiratory failure, respiratory distress or cerebral ischaemia but it is uncertain whether all the cytological changes are attributable to anoxia Gibson (1945) found no histological abnormality in the basal ganglia, pons or cortex

Haemorrhagic foci, pial-vein thrombosis and other lesions are rare and are discussed with acute encephalopathy (*vide infra*)

Pathogenesis.—The development of an altered mental state, together with fever, vomiting and circulatory disturbances, was regarded by Wilson, Macgregor and Stewart (1938) as evidence of toxaemia (Chapter 12), but it is more likely that oligaemia plays an important aetiological role, probably by reducing the cerebral blood flow, thus producing cerebral ischaemia and stagnant anoxia, and in some way raising the intracranial pressure

Oligaemia and cerebral blood flow.—The development of cerebral symptoms is usually dependent on the adequacy of intravenous therapy Gibson and Brown (1945) considered that early and adequate plasma therapy prevented stupor, restlessness and coma, whilst inadequate therapy failed to do so Morrison (1947) was impressed by the rapidity with which restlessness was relieved by intravenous therapy She found that at the time of onset of mental symptoms the haematocrit values were raised Over-transfusion was not responsible but rapid transfusion of plasma sometimes precipitated convulsions In Birmingham, Jackson (1956) finds mental symptoms uncommon during the shock period and this may be a product of energetic and well-controlled plasma therapy

The effects of oligaemia in burned patients or animals on the cerebral blood flow and oxygen consumption do not appear to have been investigated but studies have been made in the parallel field of haemorrhagic oligaemia by Stone and his colleagues (1954) The

removal of 1 5–2 2 litres of blood from professional volunteers produced considerable hypotension and mental changes such as restlessness excitement and confusion The cerebral blood flow was found to be decreased in spite of a reduced cerebral vascular resistance and the arterio-venous oxygen content difference of the blood to and from the head was increased.

Raised intracranial pressure—The necropsy findings frequently suggest a raised intracranial pressure but reports of cerebrospinal fluid pressures in burned patients are few The observations of Gibson (1945) and Morrison (1947) indicate that the pressure is raised in patients with acute cerebral symptoms during the resuscitation period Lumbar punctures performed on three patients by Gibson and on two by Morrison all showed high intraspinal pressures (250–360 millimetres of cerebrospinal fluid) and removal of 10 millilitres of cerebrospinal fluid from one of Morrison s patients had a temporary beneficial effect.

There may be a relationship between raised intracranial tension and acute vascular hypertension because all the mentally disturbed children described by Morrison developed hypertension during the resuscitation period Vascular hypertension also occurred without mental disturbance

Cerebral oedema—A number of workers have concluded that the raised intracranial pressure and the pressure effects on the brain seen at necropsy are due to cerebral oedema (Riehl 1931 Walker and Shenkin 1945 Morrison 1947) and it has already been noted that when the brain is sliced the cut surface often appears excessively wet Although the oedema is said to result from anoxia due to circulatory changes it is doubtful whether anoxia alone ever produces oedema of the brain or any tissue Furthermore the diagnosis at necropsy of generalized oedema of the brain is fraught with difficulty and doubt has been expressed whether the condition ever occurs Alternatively cerebral swelling due to hyperaemia and congestion of the brain could be responsible for the increase in pressure Walker and Shenkin (1945) thought that the perivascular and perineuronal spaces seen histologically meant oedema, but these changes are notoriously difficult to interpret in necropsy material particularly when the tissue has been processed to paraffin wax. In an attempt to settle the problem the water and chloride content in the cerebral white matter of three subjects included in Gibson s (1945) report were analysed by Anderson and Semeonoff (1945) The water content was found to be normal (68–74 per cent) and the chloride values (188–200 milligrams per 100 millilitres) were only slightly raised.

Walker and Shenkin (1945) found that the brains of patients dying of acute respiratory failure showed chromatolysis of ganglion cells, cell degeneration and even death and lysis of neurones These changes, which may be secondary to anoxia, were found in different parts of the brain but were most striking in the hypothalamus In two patients dying in acute respiratory distress following inhalation of hot air and fumes, Mallory and Brickley (1943) described degeneration of many large neurones which were often surrounded by increased numbers of satellite cells, in addition the Purkinje cells were shrunken, the oligodendroglial cells were swollen and increased in number and changes in other glial cells were found Many of the changes described by Walker and Shenkin and by Mallory and Brickley might be attributed to anoxia from respiratory failure, respiratory distress or cerebral ischaemia but it is uncertain whether all the cytological changes are attributable to anoxia Gibson (1945) found no histological abnormality in the basal ganglia, pons or cortex

Haemorrhagic foci, pial-vein thrombosis and other lesions are rare and are discussed with acute encephalopathy (*vide infra*)

Pathogenesis.—The development of an altered mental state, together with fever, vomiting and circulatory disturbances, was regarded by Wilson, Macgregor and Stewart (1938) as evidence of toxaemia (Chapter 12), but it is more likely that oligaemia plays an important aetiological role, probably by reducing the cerebral blood flow, thus producing cerebral ischaemia and stagnant anoxia, and in some way raising the intracranial pressure

Oligaemia and cerebral blood flow—The development of cerebral symptoms is usually dependent on the adequacy of intravenous therapy Gibson and Brown (1945) considered that early and adequate plasma therapy prevented stupor, restlessness and coma, whilst inadequate therapy failed to do so Morrison (1947) was impressed by the rapidity with which restlessness was relieved by intravenous therapy She found that at the time of onset of mental symptoms the haematocrit values were raised Over-transfusion was not responsible but rapid transfusion of plasma sometimes precipitated convulsions In Birmingham, Jackson (1956) finds mental symptoms uncommon during the shock period and this may be a product of energetic and well-controlled plasma therapy

The effects of oligaemia in burned patients or animals on the cerebral blood flow and oxygen consumption do not appear to have been investigated but studies have been made in the parallel field of haemorrhagic oligaemia by Stone and his colleagues (1954) The

between the groups Roth reported an extensively scalded girl of 8 years who did well for 20 days and then developed hyperpyrexia a series of convulsions and became comatose on recovery her speech was lost and she was mentally retarded Her later state reported by Bender (1943) was that of an emotionally unstable, mentally back ward girl with athetosis of the right hand and a positive right Babinski s sign The Birmingham case was a 9-year-old girl with burns on 30 per cent of the body surface who did moderately well until the twenty sixth day after burning Then she lost consciousness developed convulsions and was hyperpyrexial On recovery she had a gross loss of vision which later improved there was considerable mental defect and she became unable to read or write Her personality and behaviour changed Previously a quiet, docile child she became aggressive, restless disobedient and hostile

Pathogenesis.—Schachter argued that since encephalopathy after burns is rare there must be an associated factor He postulated that the encephalopathic state developed only when a predisposing condition such as birth trauma to the brain parental alcoholism or infection was present The clinical resemblance of many of these cases to encephalitis lethargica and its sequelae in children suggests that a true encephalitis was present However all the cases may not have the same pathology since different disease processes can give rise to similar clinical effects

Pathology—Little is known of the changes in the brain because nearly all the patients survived Globus and Bender (1936) reported the findings in an 8-year-old boy who developed a progressive mental deterioration 2 months after burning and who died 4 months later The brain showed diffuse degenerative changes in the white matter with occasional areas of perivascular demyelination and gliosis was found particularly in the subcortex The changes which were said to resemble those of multiple sclerosis, raised the possibility of acute disseminated encephalomyelitis

The author has examined the brains of 3 children with acute cerebral lesions who died soon after symptoms developed The findings may represent the acute encephalopathic processes present at an early stage in some of the other children

Case 1 —A boy of 4 years, with burns extending over 70 per cent of the body area died 5 days after the injury following a stormy clinical course which included acute haemolytic jaundice severe haemoglobinuria renal failure and coma The brain showed blurred haemorrhagic areas in the cortex and around the lateral ventricles. Histology revealed foci of haemorrhagic and non haemorrhagic cortical necrosis in which some

This problem, like that of cerebral oedema in general, has not been settled

MENINGITIS

This is a rare complication occasionally it follows burns of the scalp (Pack, 1926) but it can develop even when the head is not burned The one case of pyogenic meningitis in the author's series of 108 necropsies was in an 11-year-old girl who received burns on 40 per cent of the body surface (excluding the head) and died 6 weeks later Necropsy examination revealed a purulent meningitis from which a heavy mixed bacillary and coccal flora, including numerous *Pseudomonas pyocyanea*, was cultured The bacteria were similar to those grown from the granulating burns and it was concluded that the meningitis was blood borne

ENCEPHALITIS AND ENCEPHALOPATHY

This interesting complication is also rare and only one case occurred in Birmingham among several thousand patients admitted to the Burns Unit The patients described in the literature may be divided into two groups, (1) children in whom an acute encephalopathic episode occurred days or weeks after extensive burning, after which mental and often neurological signs of cerebral damage were present (Kruse, 1928, Globus and Bender, 1936, Schachter, 1947, 1950, Hughes, 1947), and (2) other children with psychopathic behaviour disorders apparently dating back to a burning episode years previously (Bender, 1943)

Among the first group was Kruse's case, a child of 15 months who developed convulsions and pyrexia 1 month after burning followed by temporary blindness, mental deterioration, involuntary movements and hydrocephalus, Schachter reported 4 children with mental backwardness together with aphasia, convulsions or enuresis dating from epileptiform convulsions days or weeks after a burn The children with behaviour disorders also have intellectual disability, abnormal personality development and certain neurological signs (Bender, 1943) Anti-social activity led to frequent trouble at home, at school and with the police For example a 10-year-old girl had been troublesome since she was burned 7½ years previously she was noisy, defiant and aggressive and had sex activities with a man for which she was paid she had a speech defect, anisocoria and reduced eye convergence

It is likely that the two groups are really one artificially divided by an incomplete follow-up or an incomplete history The case of Roth (1941) and another patient in Birmingham bridge the gap

non-adherent and more recent In addition a recent subarachnoid haemorrhage and haemorrhagic softening of the grey matter was present in the right frontal area and this was possibly the immediate cause of death The nature of the venous thrombosis which had obviously commenced weeks previously indicated a progressive thrombophlebitis. There was also some evidence of a diffuse encephalitic process, namely a few polymorphs scattered through the white matter small petechial haemorrhages and abnormalities of glial cells.

Although the findings in these cases differ in many respects they resemble each other in that all had one or more foci of haemorrhagic necrosis associated with thrombotic vascular lesions

PSYCHOLOGICAL EFFECTS

Like many other acutely ill people some severely burned patients become delirious mentally confused and have hallucinations This apparently toxic cerebral state usually begins some days after resuscitation, and may last days or even weeks but it is always temporary It cannot always be distinguished from the mental disorder during the shock period due to delayed or inadequate plasma therapy Like the latter state it may originate from cerebral anoxia.

Neurotic and allied sequelae are common in children and adults The neurotic disorder may produce abnormal behaviour but this differs from the encephalopathic condition in children in that there are no neurological signs there is no mental retardation (except that from loss of schooling) and the patients are amenable to psychotherapy (Bender 1943) The psychological background is usually a state of morbid anxiety or fear often with bad dreams related to reliving the burning episode or to scarring and disfigurement produced by the burns or to loss of earning capacity In a study of burned patients surviving the Coconut Grove disaster Cobb and Lindemann (1943) found that 14 out of 32 patients presented psychiatric problems Many of these were related to guilt anxiety or grief because of the loss of a dear one in the conflagration or for other reasons Two patients developed frank psychotic episodes (one jumped to death through a window) and others had various neuroses and psychoneuroses, particularly depression and anxiety states

CEREBRAL EFFECTS OF SKULL BURNS

Only when a scalp burn is deep and involves the skull can heat directly affect the brain prolonged burning by flame is necessary and consequently the condition is rare and usually fatal The usual circumstances are that during a cardiac epileptic or other cerebral

of the vessels, particularly veins, were thrombosed Their walls showed an acute fibrinoid-necrotic inflammation and contained inflammatory cells (Fig 72) Elsewhere an occasional venule was surrounded by a collar of mononuclear cells The lateral ventricles were lined by necrotic brain tissue infiltrated with leucocytes and small thrombosed vessels were present In the white matter the oligodendroglial cells were swollen and prominent

Case 2 —A girl of 8 years, with burns on 40 per cent of the body area, died 58 days after burning She was moderately well until 2 days before

FIG 72 —Periphlebitis in a necrotic focus of the cortex in Case 1 (*see text*) (Haematoxylin and eosin, × 80)

FIG 73 —Thrombosed subpial vein in Case 3 (*see text*) (Haematoxylin and eosin, × 23)

she died, then rapidly deteriorated, became unconscious and had left-sided epileptiform convulsions The brain contained a pea-sized haemorrhagic focus in the right parieto-occipital area just deep to the cortex Histologically the lesion showed multiple small often perivascular haemorrhages, recent necrosis and a loose infiltration with polymorphs A number of small vessels were irregularly cuffed by polymorphs and one contained a hyaline thrombus or embolus

Case 3 —A girl of 18 months (37 per cent burns) died suddenly on the thirty-third day Many main cerebral veins overlying the frontal and parietal parts of the convexities were thrombosed (Fig 73), some for inches, others along their whole course, and thrombi were also present in the sagittal, straight and lateral sinuses The frontal veins were white cords occluded by older organized thrombi, other veins were distended by black organizing clot whilst the sinus thrombi were

Carey and his colleagues regard the nerve muscle apparatus as a functional and morphological unit of neuromyoplasm They also believe that gold impregnation reveals normal secretory activity of the terminal axons of the end plate which they say are directly transformed *into granules and discharged into the myoplasm* They concluded that burning accentuates and aggravates the normal physiological process producing a rapid exoplasmic discharge after which the end plates and their epilemmal axons disappear Their results must be regarded with caution until they are confirmed by techniques more reliable than gold impregnation such as modern *in vivo* methylene blue preparations and histochemical demonstration of end plates by the acetylcholine technique

Nevertheless correlation of the changes found with the previous functional state of the muscle is of interest since many recently burned patients develop tonic or clonic spasm of muscles (*vide supra*) Immediately after immersion some rats had severe muscle spasms or convulsions which resulted in tonic extensor rigidity others had mild twitching followed by strong fascicular shivering movements Later many animals had flaccid paralysis of one or more extremities These authors correlated muscle spasm with excessive gold impregnation of the end plates and with gold impregnated material in the myoplasm which they interpret as excessive neural discharge the later weakness or palsy was associated with loss of stainability of the end plates and epilemmal axons which they say means exhaustion

REFERENCES

Anderson, A. B., and Semeonoff, E. (1945) In *Studies of Burns and Scalds* p. 183 M R.C. Special Report Series No 249

Bender L. (1943). *Arch. Pediat.*, 60, 75

Carey E. J., Massopust, L. C. Zelt, W., and Haushalter E. (1946) *Amer J Path.*, 22, 175

Cobb S and Lindemann, E. (1943) *Ann Surg.*, 117 814

Elman, R. (1944) *Ann Surg.*, 120, 211

Gibson, T (1945) In *Studies of Burns and Scalds* p 192. M R.C Special Report Series No 249

— and Brown, A. (1945) *Ibid* p 49

Globus J H and Bender M B (1936). *J nerv ment Dis* 83 518

Hughes, L. (1947) *Med J Aust* 2, 122.

Jackson, D McG (1956) Personal communication.

Keeley J L Gibson, J E., and Pijoan, M (1939) *Surgery* 5, 872.

Kruse F (1928) *Med Wschr.*, 54, 1039

Mallory T B and Brickley W J (1943) *Ann Surg* 117 865

Morrison, Brenda (1947) *Arch Dis Childh.*, 22, 179

Pack, G T (19 6) *Arch. Path. (Lab Med)* 1 767

Riehl, G (1931). *Arch. Derm. Syph.*, 164, 409

Rosenthal, S M., and Tabor H (1945) *Arch Surg* 51 44

attack, the victim collapses, his head falls into an open fire and later he is found dead or unconscious

In the worst cases the whole thickness of the skull is charred, the dura is burned and part of the brain is cooked Fortunately such patients are usually found dead In others the outer table of part of the skull is charred, the inner table and dura appear normal but deep to the burned area the brain shows subarachnoid haemorrhage and large irregular areas of haemorrhagic necrosis (Fig 74) Histologically there are confluent or semiconfluent areas of haemorrhagic necrosis, the cortical neurones and other nerve cells are destroyed and in the white matter the axis cylinders have disintegrated, appearing as ghost-like forms in silver preparations Numerous empty

FIG 74 —Burn of skull with charring of outer table The underlying brain shows subarachnoid and intracerebral haemorrhage Patient had a coronary thrombosis and fell into an open fire

vesicle-like spaces may be found, possibly the effects of steam The surrounding brain is congested, oedematous and contains numbers of petechial haemorrhages The presence of a large spontaneous cerebral haemorrhage, coronary thrombosis or a cerebral tumour indicates the origin of the disaster

MOTOR END-PLATES AND INTRAMUSCULAR AXONS

The effects of burning on motor end-plates and intramuscular nerves were studied by Carey and his colleagues (1946) in gold-impregnated muscle preparations from scalded rats Within seconds of burning there was an increased intensity of gold impregnation and 1–3 hours later there was a loss of impregnation of the plates, culminating in a complete absence of staining This was said to be due to the absence of the terminal axonic structures, which had undergone granular disintegration and dispersion in the myoplasm

CHAPTER 21

GASTRO INTESTINAL TRACT

VOMITING is very common in extensively burned patients, haematemesis may occur and a phase of melaena is frequent At autopsy lesions in the stomach duodenum and bowel may be present. Part of or even the whole gastro-intestinal tract may be hyperaemic, mucosal petechiae are common and there may be extensive areas of mucosal haemorrhage in the intestine Some patients develop acute erosions in the gastric mucous membrane and some a duodenal ulcer

THE STOMACH

Vomiting and gastric motility —During the first 2 or 3 days repeated and troublesome vomiting is common in patients with large burns and this often interferes with oral fluid therapy Plasma or other colloid transfusion does not influence the vomiting (Gibson and Brown 1945 Markley and his colleagues, 1956) but the latter workers stated that vomiting was not troublesome in patients treated with massive doses of oral saline without intravenous therapy

There is evidence that excessive gastric contraction and movement occurs after burning (Necheles and Olson 1942) and that the emptying is delayed (Cordier and Pérès 1951) Working with dogs, Necheles and Olson (1942) showed that shortly after burning the motility of the stomach and duodenum increased, particularly at the pyloric end and that tonic contraction waves at the rate of 1–2 per minute reduced the stomach to half its previous size The excessive movement was abolished by the administration of atropine but not by section of the splanchnic nor vagus nerves, and therefore an increased acetylcholine activity could explain the excessive movement The evidence of a delay in gastric emptying is based on the rate of disappearance of glucose solution from the stomach of burned rats (Cordier and Pérès, 1951) When glucose was introduced into the stomachs of normal rats little or none was present 12 hours later but when it was introduced 2–12 hours after burning a considerable amount was still present 12 hours later This may have resulted from pyloric contraction Taken together the evidence suggests that post burn vomiting in man results from an excessive contraction and motility of the stomach

Roth, N (1941) *Arch Neurol Psychiat*, **45**, 980
Schachter, M (1947) *Ann Paediat*, **168**, 105
— (1950) *Acta Psychiat*, *Kbh*, **25**, 285
Stone, H H, MacKrell, T N, Brandstater, B J, Haidak, G L, and Nemir, P (1954) *Surg Forum*, **5**, 789
Walker, J, and Shenkin, H (1945) *Ann Surg*, **121**, 301
Wilson, W C, Macgregor, A R, and Stewart, C P (1938) *Brit J Surg*, **25**, 826

Congestion and petechiae.—Congestion and swelling of the gastric mucosa in burned patients was recorded many years ago by Cumin (1823) Dupuytren (1832) Curling (1842) and others and has been repeatedly confirmed in man and animals (for instance by Pack, 1926 Erb Morgan and Farmer 1943 Hartman 1945 Friesen and Wangensteen 1947) The hyperaemia also involves the duodenal mucosa and is part of the generalized visceral congestion which develops within a few hours of burning The whole mucous membrane may be rose pink in appearance and spotted with fine haemorrhages The latter may be closely set and warrant the name of a petechial eruption but sometimes they are scattered and few Petechiae may

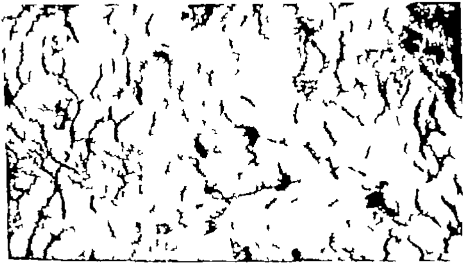


FIG 75.—Multiple tiny erosions in the gastric mucosa (× 4)

be found all over the stomach but are commonly concentrated either in the fundus around the cardia or in the body and less often in the pylorus Occasionally the stomach contains some tarry blood or a chocolate-coloured sero-sanguinous effusion even in the absence of erosion

Erosions of the mucosa.—In a minority of patients the haemorrhagic congestion is accompanied by superficial ulceration The author has found this in 9 out of 108 subjects (8 3 per cent) 7 of whom died 12 hours to 6 days after burning but only one of whom had duodenal ulceration The gastric ulceration is confined to the mucous membrane unlike that in the duodenum and varies from one two or more irregular eroded areas 1–5 centimetres in diameter to multiple tiny ulcers scattered all over the stomach (Fig 75) sometimes these

Gastric secretion.—The gastric juice is of special interest because of its likely connexion with duodenal ulceration Some of the results concerned with the volume and acidity of the gastric juice are contradictory, but the discrepancies reported may be more apparent than real because there is evidence that intravenous therapy affects the secretion Necheles and Olson (1942) studied the effects of burning on the gastric juice of dogs during the first few hours after injury Burning was followed by only a slight increase in gastric secretion and no change in the acid content, but when intravenous saline or glucose solution was transfused the volume of the juice increased greatly and free hydrochloric acid appeared On the other hand Friesen (1950) found little or no change in the volume or free acid content of the juice of dogs either immediately after burning or a few days later, and Hartman (1945) found no evidence of hyperchlorhydria when the dogs were tested a week after burning, however, neither of these workers examined the effect of transfusion

Necheles, Prescott and Olson (1946) showed that the increase in the gastric secretion of their burned, transfused dogs was not suppressed by atropine and they considered that the added secretion may have resulted from the liberation of histamine They suggested that the administration of an antacid, with atropine to inhibit gastric motility, may prevent vomiting and gastroduodenal ulceration in burned patients

Apparently the only mention of gastric analyses in patients is that by Wilson, Macgregor and Stewart (1938) who noted that the total acidity was always reduced, that hypochlorhydria was common and that hyperchlorhydria never occurred Few of their patients were treated with plasma and it is uncertain whether the observations were made on transfused or untransfused subjects

Haematemesis—The vomiting of blood during the first 2 days is usually found among those who are badly burned and has a serious prognosis The vomit usually has a "coffee-ground" appearance due to alteration of the blood, but fresh blood may be vomited At necropsy early haematemesis is rarely explained by duodenal ulceration and is usually associated with haemorrhagic lesions or erosions of the gastric mucosa After the shock period vomiting of blood is much less common but is then often due to duodenal ulceration

Post-mortem findings—Congestion, fine haemorrhages and swelling of the gastric mucosa are common and superficial erosions are not infrequent

Morbid anatomy —The site of ulceration is nearly always the posterior surface of the first stage of the duodenum within an inch of the pyloric sphincter (Fig 76) Double ulcers are as common as single ones and sometimes 3 or 4 are found When two are present they are commonly situated posteriorly but sometimes one is posterior and the other anterior or superior Ulcers have also been reported more distally and in the second stage of the duodenum (for instance by Jayesuria and Marsden 1949) but they are rare The ulcers are small and circumscribed usually measure 3–10 millimetres across and are commonly oval or irregular in outline The edge is clear-cut or slightly rolled and there is no peripheral induration The ulcer always penetrates the submucosa, usually erodes into the muscle layer and

FIG 76.—Duodenal (Curling's) ulcer after burning. The crater is deep and is situated within 1 inch of the pyloric sphincter (U = ulcer)

may penetrate to the serosa or through to the head of the pancreas In such cases it is the posterior location together with the small size of the ulcer which prevents clinical perforation The floor of the ulcer is sometimes covered by blood clot and careful inspection may then reveal the exposed ends of one or two small arteries In patients with recent haematemesis or severe melaena erosion of larger branches of the pancreatico-duodenal artery may be visible

The first stage of the duodenum occasionally shows a thin puckered scar presumably the healed remains of an ulcer but it may be impossible to decide whether this preceded or followed the burning A healed mucosal lesion was found by the author in a patient who died 11 days after burning but this was not included as a post burn ulcer

Histological appearance —The mucosal edge is usually sharp and abrupt but a little undermining may be present Inflammatory

are pin-head in size but they may vary from 1 to 4 millimetres in diameter The mucosa may be lined by a fibrinous or mucous exudate when the process may be termed ulcero-gastritis Oesophageal erosions have also been reported A fatal case of burns associated with massive gastric haemorrhage apparently from 3 recent mucosal erosions was reported by Miln and Ross (1946)

DUODENAL ULCERATION

The gastro-intestinal lesion which has aroused most interest is duodenal ulceration, probably because of its potentially wider significance Following the account of Curling (1842) the condition became known as Curling's ulcer but his report was preceded by those of Swan (1823), Dupuytren (1832), Cooper (1839) and Long (1840) Various workers, including Curling (1842), Perry and Shaw (1894), Thiele (1919) and Harkins (1938), have collected and reviewed cases from the literature Harkins reviewed over 80 cases verified by autopsy as well as others with gastric ulceration Since then reports of a number of cases among a series of subjects studied at necropsy have been made by Wilson, Macgregor and Stewart (1938), Noland and Wilson (1940), Erb, Morgan and Farmer (1943) and Gibson (1945) (Table III) The continued reporting of individual cases (for example by Lozano, 1947, and Jayesuria and Marsden, 1949) would suggest that the condition is rare, as would the fact that the author's series of 8 cases is larger than any reported series The rarity is more apparent than real because few pathologists have the opportunity to examine a sufficiently large number of fatally burned subjects

TABLE III

Frequency of duodenal ulcer among burned subjects at autopsy

Authors	*No of patients* with ulcers / total in series	*Percentage with ulcer*
Wilson, Macgregor and Stewart (1938)	4/33	12 2
Noland and Wilson (1940)	2 11	18 2
Erb, Morgan and Farmer (1943)	5/61	8 2
Gibson (1945)	3/30	10 0
Sevitt (Unpublished observation)	8/108	7 5
Total	22/243	9 0

(1938 1942) estimated the necropsy frequency as only 3 8 per cent This was based on 25 cases of ulcer among 676 subjects submitted to necropsy reported by 11 authors from Long in 1840 to Riehl (1930) and included another which Harkins found among 4 autopsied subjects A few were gastric and not duodenal ulcers

The present apparently higher incidence of ulceration may reflect the longer survival of more extensively burned patients Plasma transfusion has made it possible for many extensively burned patients who previously died during the shock period to survive the first 2–4 days and to live during the period of ulceration during which many of them die from other causes Transfusion may contribute to the increased incidence in another way By allowing the volume and free acid content of gastric juice to increase (Necheles and Olson 1942) intravenous transfusion may precipitate ulceration more frequently On the other hand it would reduce the degree and duration of haemoconcentration which Friesen (1950) claims predisposes to gastroduodenal lesions

Duodenal ulcers are found at all ages and in both sexes but the absolute numbers of women and children affected are respectively greater than the numbers of men or adults This is mainly because the frequency of domestic accidents results in more children and women being fatally burned

Pathogenesis.—Numerous theories have been advanced to explain the ulceration These include the effect of toxins, increased secretion of histamine, gastric acidity adrenal failure fat emboli septic emboli infection thrombosis capillary stasis dehydration haemoconcentration shock and nervous influences but many of these ideas are unsupported by facts and will not be considered

The most probable explanation of duodenal ulceration is that two factors, precipitating and underlying causes are responsible

Precipitating factor —The location of the ulcers within an inch of the pyloric sphincter suggests that the acid peptic activity of gastric juice erodes a part of the mucosa the vitality of which has been reduced by some underlying mechanism This is supported by the work of Friesen (1950) who showed first that stimulation of gastric secretion in extensively burned dogs by administration of histamine (in beeswax) greatly increased the frequency of ulceration and secondly that subtotal gastrectomy of animals later subjected to burning (plus histamine administration) prevented duodenal ulceration

Underlying cause —The manner by which the duodenum is predisposed to ulceration is not known but most workers agree that

changes are slight but the muscle coat remaining in the base may show early fibroblastic invasion and a loose infiltration of lymphocytes polymorphs and eosinophil leucocytes There is rarely evidence of capillary or arteriolar thrombosis The histology indicates that the ulcer resulted from the erosion of an acute localized lesion Sometimes there is evidence of healing

Complications.—Most of the cases produce no symptoms but sometimes haemorrhage or perforation occurs

Haemorrhage —As has been mentioned *early* haematemesis and melaena usually result from gastric lesions but duodenal ulceration is often responsible when bleeding commences some days after burning Occasionally a massive haemorrhage occurs and may prove fatal or contribute to death Such bleeding is usually due to erosion of the pancreatico-duodenal artery or one of its main branches

Perforation —Clinical perforation is rare although numbers of cases have been reported (Koch and Fischer 1945, Ramsey and Mosquera, 1947, Peer, 1949, Mynhardt, 1951) It is usually associated with an anteriorly situated ulcer and then peritonitis may develop Peritonitis is not invariable because the small ulcer may collapse, the edges may approximate and the serosa become sealed off by fibrinous exudate and omental adhesions

Onset and frequency.—Duodenal ulceration is rare in patients who die during the shock phase and the evidence suggests that it develops later The times of death of 71 reported subjects with duodenal ulcers at necropsy reveals that only one died within 2 days of burning, 4 died between 2 and 4 days, 16 between 4 and 8 days, 28 between 8 and 14 days and 22 died after this period Similarly among 199 fatally burned patients (Erb, Morgan and Farmer, 1943, Gibson, 1945, and the author's series) duodenal ulceration was not found in any of the 55 patients who died within 2 days of burning whilst it was present in 16 of the 144 patients dying after 2 days

The true incidence of duodenal ulcer is impossible to determine because the condition rarely produces symptoms unless haemorrhage or perforation occurs, otherwise it comes to light only at necropsy The incidence of ulcers which form and heal among survivors is also unknown

Table III sets out the incidence at necropsy and shows that the over-all frequency of duodenal ulcer is about 9 0 per cent among fatally burned patients The estimate is based on 22 cases of ulcer found at necropsy among 243 subjects in 5 series reported since 1938 Taking into account the small numbers in each series there is moderately good agreement between them On the other hand Harkins

motion the changes which lead to gastroduodenal lesions The relationship between nervous lesions and peptic ulceration was raised by Cushing (1932) who found ulcers in patients with lesions in the hypothalamus and the interrelationship between the posterior pituitary the hypothalamus and the gastroduodenal mucosa (Dodds Noble and Smith, 1934 Nedzel 1938) is consistent with the nervous theory Search by the author for cerebral lesions in fatally burned patients has shown hyperaemia and swelling of the cerebrum a perivascular and pericellular oedema and sometimes small haemorrhages into the Virchow Robin spaces but these changes also occur in subjects without duodenal ulceration The hypothalamus is commonly affected and in burned dogs Hartman (1945) also found vascular changes in this area and small necrotic foci in one animal. The nervous theory has been supported by Verdan (1945) who found perivascular lymphocytic collections in the arachnoid in one patient.

A connexion between hypersecretion of ACTH and adrenocortical steroids with peptic ulceration is also possible since administration of ACTH or cortisone may produce acute gastric or duodenal ulceration in normal subjects (Hirschowitz, Pollard and Boldt 1955 Hirschowitz and his colleagues 1956) or exacerbate healed or healing ulcers Therefore endogenous hormone activity in response to burning may initiate an ulcer

THE INTESTINE

Occult blood in the faeces is often found in patients with large burns particularly during the first week and occasionally frank melaena occurs Gastroduodenal haemorrhage may contribute to this but the lesion usually responsible is a diffuse leaking of blood from the mucous membrane of the bowel

Post-mortem findings.—The mucous membrane of much of the intestine, particularly the ileum is commonly swollen and hyperaemic in those who die during the first few days after burning In some patients there is also a diffuse submucosal and mucosal haemorrhage the degree and extent of which varies from patient to patient. The lining of the bowel may have a dark red, chocolate-coloured or blackish appearance In most of those affected the ileum particularly the terminal part is more haemorrhagic than the jejunum (Fig. 78) in some cases both the ileum and colon (particularly the caecum and ascending colon) are considerably haemorrhagic and in others only the ileum or the large bowel is affected In such patients the haemorrhage stops short at or commences just beyond the ileo-caecal junction (Fig. 77)

Usually the contents of the bowel are not visibly haemorrhagic

early mucosal congestion or tissue changes associated with congestion is the precursor to acute ulceration In this, three factors are possibly involved (1) haemoconcentration, (2) infection, and (3) neuro-humoral stimulation

(1) *Haemoconcentration* —On the basis of experimental work in dogs Friesen (1950) believed that haemoconcentration *per se* is the main factor predisposing to ulceration of the stomach and duodenum He suggested that the increased viscosity of the blood resulted in congestion and a decreased blood flow which lowered the viability of the duodenal and gastric mucosa, thereby allowing gastric juice to produce ulceration Wilkie (1911) had previously suggested that the vascular supply to the duodenum was precarious and that interference by thrombosis, stasis, pressure or other means lowered the vitality of the mucosa Friesen established that post-burn haemoconcentration in dogs was closely associated with the development of gastric and duodenal congestion, erosions and ulcers (when gastric secretion was stimulated by histamine) and found that when haemoconcentration was prevented by transfusion of plasma gastroduodenal lesions failed to occur In unburned dogs haemoconcentration without dehydration or oligaemia was often achieved by repeated withdrawal of blood followed by re-injection of the same volumes freed of plasma In such animals administration of histamine regularly produced mucosal congestion and ulceration but failed to do so when haemoconcentration was not produced by this experimental method

(2) *Infection* —Acute duodenal ulcer has been attributed to infection or sepsis partly on statistical grounds and partly through experimental work Stewart (1923) reviewed 53 cases of acute peptic ulcer in 15,000 consecutive necropsies and found that acute sepsis was present in about half of these Bacterial infection of burns is so common that it is easy to establish a positive correlation between infection and ulceration but it is probably just as easy to establish a link between infection and absence of ulceration Moreover duodenal ulceration has not decreased in frequency and may have increased in recent years (*vide supra*) and during this period chemotherapy has been introduced against bacterial infection In Birmingham there is a considerable attack against infection and yet the incidence of duodenal ulceration is relatively high

The experimental work of Hartman (1945, 1946) lends some support to the theory of infection He found that 63–77 per cent of severely burned dogs developed duodenal ulcers, the incidence was only 23 per cent in those receiving injections of penicillin but tannic-acid therapy lowered the frequency to 6 6 per cent Friesen (1950) could not confirm this work and was unable to protect burned dogs against gastro-duodenal ulceration by large doses of penicillin

(3) *Neuro-humoral factors* —Since visceral congestion is prevented by prior section of the nerve supply in the burned area or of the spinal cord (Brown-Séquard, 1858) nervous stimulation from the burn may set in

but a sero-sanguinous effusion may be present, particularly in the small intestine and the formed faeces are occasionally blackened

The Peyer's patches are prominent and swollen especially in children and occasionally they may be superficially ulcerated mucosal erosions elsewhere are rare but have been reported

REFERENCES

Brown-Séquard, E. (1858) *Lancet* 2, 545
Cooper C. (1839) *London Med Gaz.*, 23, 837
Cordier D and Pérès, G (1951). *Compt Rend Soc Biol.*, 145, 399
Cumin, W (1823). *Edinb Med Surg J.*, 19 337
Curling, T B (1842) *Med. Chir Trans Lond.*, 25, 260
Cushing, H. (1932) *Surg Gynec Obstet* 55, 1
Dodds, E. C., Noble, R L., and Smith, E. R. (1934). *Lancet* 2, 918
Dupuytren, A (1832) *Leçons orales de clinique chirurgical* Paris
Erb I. H., Morgan, E. M and Farmer A W (1943) *Ann Surg* 117 234
Friesen, S. R (1950) *Surgery* 28, 123
— and Wangensteen O H (1947) *Proc Soc exp Biol Med* 64, 81
Gibson, T (1945) In *Studies of Burns and Scalds* p 192. M R C Special Report Series No. 249
— and Brown, A. (1945) *Ibid.* p 49
Harkins, H. N (1938) *Surgery* 3, 608
— (1942) *The Treatment of Burns* Springfield Thomas.
Hartman, F W (1945). *Ann Surg.*, 121 54
— (1946) *Gastroenterology* 6, 130
Hirschowitz, B. I., Pollard, M H. and Boldt, H A (1955) *J Amer med Ass.*, 158, 27
— Streeten, D H. P., London, J A. and Pollard H M (1956) *Lancet* 2, 1081
Jayesuria, L. W., and Marsden, A. T H (1949) *Brit med., J* 1 1123
Koch, V W., and Fischer W A. (1945). *Ann. intern med.*, 22, 719
Long, J (1840) *London Med. Gaz.* 25, 743
Lozano D V (1947) *Rev Policlinic Caracas* 16, 142.
Markley, K., Bocanegra, M Bazan, A. Temple, R., Chiappori, M., and Morales, G (1956). *J Amer med Ass* 161 1465
Miln, D C., and Ross, M S (1946). *Glasg med J.*, 27 203
Mynhardt, M R. (1951) *S Afr med J.*, 25, 114
Necheles, H and Olson, W H. (1942) *Surgery* 11 751
— Prescott, E., and Olson, W H (1946). *Ibid.*, 20 382.
Nedzel, H J (1938) *Arch Path.* 26, 988.
Noland L., and Wilson, C. H (1940) *J med Ass Ala* 10 157
Pack, G T (1926) *Arch. Path Lab Med.* 1 767
Peer H (1949) *Klin Med.*, 3, 814.
Perry E. C., and Shaw L. E. (1894) *Guy's Hosp Rep.*, 50 171
Ramsey, T L. and Mosquera V T (1947) *Ohio med J* 43, 276
Riehl G (1930). *Acta derm venereol Stockh.* 11 277
Stewart, M J (1923). *Brit med J.*, 2, 955 1021
Swan, J (1823). *Edinb med J* 19 344
Thiele, P (1919). *Ergebn inn Med Kinderh.*, 16, 302.
Verdan, C (1945) *Gastroenterologia*, 70 57
Wilkie, D (1911) *Surg Gynec Obstet.*, 13 399
Wilson, W C., Macgregor A. R., and Stewart, C P (1938) *Brit J Surg* 25 826

FIG 77 —The mucosa of the colon is black with haemorrhage which commenced just beyond the ileo-caecal junction The ileum is normal

FIG 78 —Diffuse haemorrhage into the mucosa of the ileum

liver and to the healing skin and was gradually abandoned during the last war Although now of historic interest the story of tannic acid may have relevance to other drugs

The danger of tannic acid therapy was first suspected by Dunbar (1934) who found that the death rate was twice as high among those treated by tanning as among other burned patients Centrilobular necrosis of the liver often with overt or latent toxic jaundice was later reported in tanned patients but was considered to result from toxaemia or anoxia (Wilson Macgregor and Stewart 1938 Belt 1939 Buis and Hartman 1941) Later the *propter hoc* relationship of the liver necrosis to tanning was suspected by Wilson (1942) who showed that tannic acid was toxic to animals, and he questioned whether absorption from the treated skin might account for the "toxaemia seen in many patients At the same time Wells Humphrey and Coll (1942) showed that liver necrosis developed in rats injected subcutaneously with tannic acid and that this was comparable with the liver necrosis found in fatally burned tanned patients The toxicity of tannic acid for various experimental animals was confirmed by other workers (Barnes and Rossiter 1943 Clark and Rossiter 1943 Hartman and Romence, 1943 Cameron Milton and Allen 1943) Rossiter and his colleagues showed that tannic acid impaired liver function as measured by the galactose tolerance test that after tanning an animal s burned skin tannic acid was found in the internal organs including the liver and that tanning increased the fatality rate of burned animals and produced centrilobular liver necrosis or severe degeneration

Liver function was investigated by Rae and Wilkinson (1944) in burned children treated with tannic acid jelly Abnormal laevulose tolerance tests were found in 5 out of 8 children so treated even though their burns were relatively restricted averaging only 5 per cent of the body area

The frequency of hepatic necrosis reported in different series of fatally burned patients tanned and untanned is shown in Table IV For example 25 of the 41 tanned patients studied by Erb Morgan and Farmer (1943) showed liver necrosis but this was not found in the 20 untanned subjects and out of 33 tanned patients reported by Wilson Macgregor and Stewart (1938) there was severe liver degeneration or necrosis in 14 and slight liver changes in a further 6 Cessation of tannic acid therapy was reflected in reports which showed hepatic necrosis to be infrequent for example only 2 of the 30 necropsy subjects reported by Gibson (1945) had hepatic necrosis In Birmingham tannic acid is not used and liver necrosis is rare in the author s experience Table IV shows that liver necrosis occurred in

CHAPTER 22

THE LIVER AND GALL-BLADDER

HEPATIC pathology in burned patients was complicated by the introduction of tannic acid therapy (Davidson, 1925) the result of which was a relatively frequent centrilobular necrosis and overt or latent jaundice Prior to the introduction of tannic acid histological changes had been reported in the liver of fatally burned subjects, but necrosis was infrequent and slight and the effects were generally restricted to fatty change, cloudy swelling or other forms of degeneration At that time the importance of oligaemia was not recognized, patients were not transfused and many developed peripheral circulatory failure The hepatic blood flow would probably have been affected and it is possible that the histological changes in those dying within a few days of burning resulted from hepatic hypoxia of circulatory origin Nowadays in adequately transfused patients this is a less likely cause of liver disturbance, many patients live longer than previously and are more frequently exposed to other causes of hepatic impairment These include lack of food during the shock period, bacterial infection, metabolic changes related to the katabolic loss of flesh, the action of certain drugs and anaesthetic agents and virus hepatitis from plasma transfusion A minor degree of hepatic necrosis still occurs but is infrequent, whilst fatty change is relatively common Some degree of liver dysfunction can often be established by laboratory tests but there is no certain evidence that liver failure contributes to death or plays an important role in the burn illness Nevertheless further investigation is required and in particular serial blood ammonium studies are needed The role of the liver in carbohydrate and nitrogen metabolism after burning is dealt with in Chapter 17 Before considering the liver changes which may follow burning the influence of tannic acid therapy will be discussed

LIVER NECROSIS AND TANNIC ACID THERAPY

Davidson (1925) advocated the spraying or painting of the burned surface with a solution of tannic acid in order to coagulate the proteins of the burned skin and thereby prevent the absorption of "toxic products" After years of use tanning was proved to be toxic to the

liver and to the healing skin and was gradually abandoned during the last war Although now of historic interest the story of tannic acid may have relevance to other drugs

The danger of tannic acid therapy was first suspected by Dunbar (1934) who found that the death rate was twice as high among those treated by tanning as among other burned patients Centrilobular necrosis of the liver often with overt or latent toxic jaundice, was later reported in tanned patients but was considered to result from toxaemia or anoxia (Wilson Macgregor and Stewart, 1938 Belt, 1939 Buis and Hartman 1941) Later the *propter hoc* relationship of the liver necrosis to tanning was suspected by Wilson (1942) who showed that tannic acid was toxic to animals and he questioned whether absorption from the treated skin might account for the toxaemia seen in many patients At the same time Wells, Humphrey and Coll (1942) showed that liver necrosis developed in rats injected subcutaneously with tannic acid and that this was comparable with the liver necrosis found in fatally burned tanned patients The toxicity of tannic acid for various experimental animals was confirmed by other workers (Barnes and Rossiter 1943 Clark and Rossiter 1943 Hartman and Romence 1943 Cameron Milton and Allen 1943) Rossiter and his colleagues showed that tannic acid impaired liver function as measured by the galactose tolerance test, that after tanning an animal s burned skin tannic acid was found in the internal organs including the liver and that tanning increased the fatality rate of burned animals and produced centrilobular liver necrosis or severe degeneration

Liver function was investigated by Rae and Wilkinson (1944) in burned children treated with tannic acid jelly Abnormal laevulose tolerance tests were found in 5 out of 8 children so treated even though their burns were relatively restricted averaging only 5 per cent of the body area

The frequency of hepatic necrosis reported in different series of fatally burned patients tanned and untanned, is shown in Table IV For example 25 of the 41 tanned patients studied by Erb Morgan and Farmer (1943) showed liver necrosis but this was not found in the 20 untanned subjects and out of 33 tanned patients reported by Wilson Macgregor and Stewart (1938) there was severe liver degeneration or necrosis in 14 and slight liver changes in a further 6 Cessation of tannic acid therapy was reflected in reports which showed hepatic necrosis to be infrequent for example only 2 of the 30 necropsy subjects reported by Gibson (1945) had hepatic necrosis In Birmingham tannic acid is not used and liver necrosis is rare in the author s experience Table IV shows that liver necrosis occurred in

over 50 per cent of fatally burned tanned patients but it was found in only about 3 per cent of the patients not treated with tannic acid

TABLE IV

Hepatic necrosis and tannic acid therapy in fatally burned patients

Reference	*Tannic acid therapy* No with liver necrosis / total in series	*No tannic acid therapy* No with liver necrosis / total in series
Wilson, Macgregor and Stewart, 1938	14/33	—
Buis and Hartman, 1941	4/5	—
Erb, Morgan and Farmer, 1943	25/41	0/20
Wells, Humphrey and Coll, 1942	4/8	—
Jackson, 1944	2/3	0/4
Gibson, 1945	—	2/30
Baker, 1945	—	0/28*
Gillman and Gillman, 1948	—	?1/38
James, Purnell and Evans, 1951	—	1/5
Total	49/90 (54%)	4/125 (3%)

* Necrosis found in 8/87 patients but only in 28 was tannic acid not definitely used

Histology.—The characteristic histological picture is necrosis of the central parts of the liver lobules, often associated with haemorrhage and infiltration with leucocytes In some patients mid-zonal necrosis was reported (Belt, 1939) In severe cases only a narrow strip of normal liver substance surrounded the portal tracts and the remainder of the parenchyma was completely necrotic

Other drugs —Tannic acid is not the only cause of liver dysfunction in burned patients but it is or was the most frequent, although there is evidence that locally-applied sulphonamides may impair liver function (Rae and Wilkinson, 1944) They found that at least 2 out of 7 children whose burns were treated with a paste containing sulphacetamide had abnormal laevulose-tolerance tests and thought that sulphonamides should be used with caution on large burned surfaces It is known that many substances, including sulphonamides, penicillin, aureomycin, and lactose, are rapidly absorbed from a burned surface and it is possible that local sulphonamide therapy sometimes leads to toxic concentrations in the blood

There is experimental evidence that subcutaneous injection of

silver nitrate or ferric chloride solution in burned dogs is hepatotoxic (Hartman and Romence 1943) although Rae and Wilkinson (1944) found that liver function was less often impaired in burned children treated with local silver nitrate than in those treated with local tannic acid or sulphacetamide

LIVER CHANGES AFTER BURNING

Necropsy findings.—Histological changes in the liver had been reported in the pre tannic acid period (Bardeen 1897 Weiskotten 1919 Olbrycht, 1924) but zonal necrosis was uncommon Weiskotten found small foci of necrotic liver cells in 2 out of 10 patients The occasional case of definite hepatic necrosis which occurs in untanned subjects can sometimes be related to severe bacterial infection or other causes The 3 most advanced cases in the series of Baker (1945) had various infections and one of Gibson s (1945) two patients had streptococcal septicaemia (Table IV) A slight degree of necrosis may result from burning presumably from circulatory ischaemia, and changes of this kind were reported by Zinck (1940) In extensively burned dogs dying 4–10 days after burning Hartman and Romence (1943) found considerable congestion of the sinusoids and compression of the liver cords with granular vacuolar and fatty degeneration of the liver cells Some centrilobular necrosis was found in many of those who died later Sinusoidal congestion and liver-cord compression or atrophy may be found in patients and degenerative changes of the liver cells, including cloudly swelling, are not infrequent. Some workers have found no histological evidence of liver damage An early atrophy of the central liver cells with loss of basiphilia and staining ability and occasional fat free vacuoles were reported by Gillman and Gillman (1948)

Fatty change—A number of workers have been impressed with the frequency and severity of fatty change (Gibson, 1945 Baker 1945 Gillman and Gillman 1948 Monsaingeon 1952) and examination by the author of 108 livers of fatally burned patients has confirmed this Fatty change may be found in patients who die during the first few days after burning and in those who die days or weeks later Gibson (1945) reported that 5 of the 11 subjects who died during the "shock period" had fatty livers and that the degree of fatty change was roughly related to the length of survival He also found fatty livers in 2 out of 11 patients who died at a later stage Baker (1945) found fatty livers in 8 out of 41 patients dying within 2 days and in 11 out of 25 patients dying later than the second week Hepatic fat was also noted by Gillman and Gillman (1948) in those who died 14–3 days after burning and in those who survived 10 days or longer

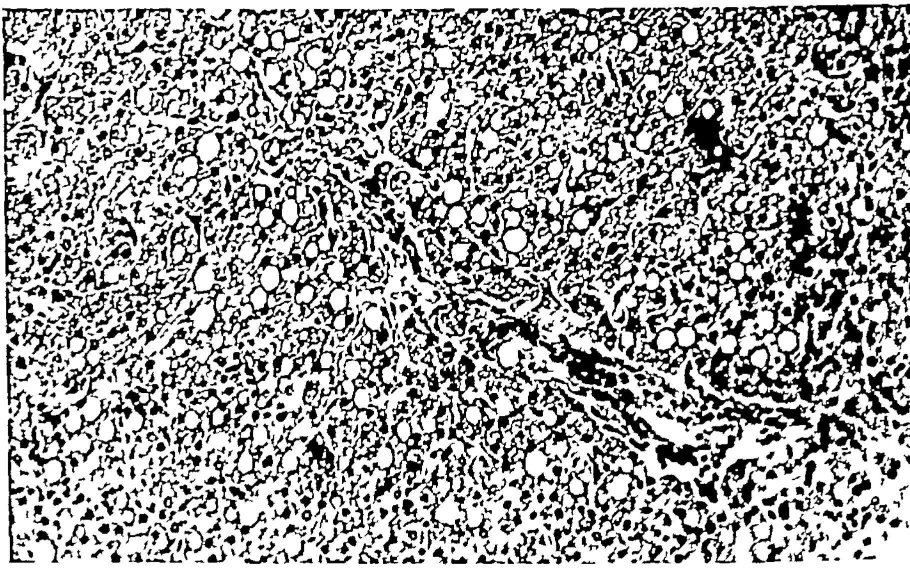


FIG 79 —Periportal fatty changes in the liver From a girl aged 3 years who died 17 days after burns on 12 per cent of her body area The fat has been dissolved out and is represented by empty spaces (Paraffin section, haematoxylin and eosin, × 140)

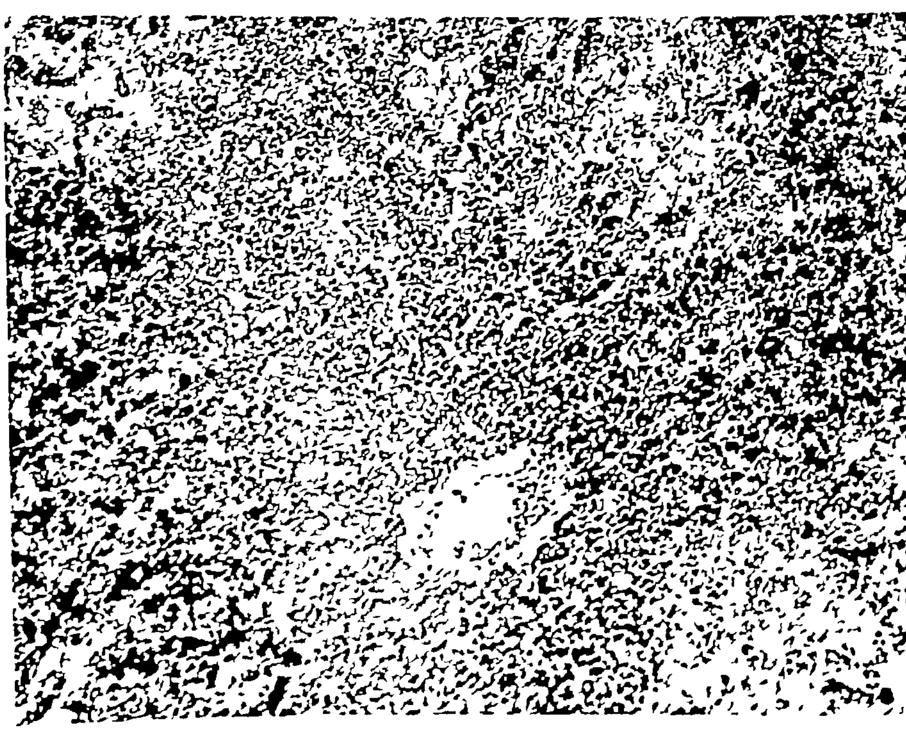


FIG 80 —Centrilobular fatty changes in the liver From a boy aged 4 years who died 41 days after burns which involved 70 per cent of his body surface Heavy black indicates fat globules (Frozen section stained oil red O, × 100)

According to them the distribution of the fat within the hepatic lobules differed with length of survival it was centrilobular in patients who died early and mainly periportal in those who died later This suggested that two different metabolic effects were involved Monsaingeon (1952) was also impressed with the degree of fatty change found in the livers of patients who died late 2 or 3 months after burning, and reported that the fat was centrilobular in distribution He believed this to be metabolic in origin not related to infection or toxaemia and he associated the stéatose hepatique

FIG 81 —Liver showing Kupffer cells laden with haemosiderin. From a girl aged 9 years who died 4½ days after burns which involved 55 per cent of the body surface. The multiple fine black streaks and dots lining the sinusoids between the unstained liver parenchyma cells indicate haemosiderin. (Prussian blue 150.)

with the loss of flesh and katabolic response of the patient In the author s experience there is no constant zonal pattern of fatty change with any length of survival (Figs 79 and 80) Fatty change is well known to occur in starvation and the early appearance of fat may be related to the lack of food intake during the shock phase Alternatively acute hepatic hypoxia from a disturbance of the blood flow may be responsible for the early appearance of fat (*vide infra*)

Kupffer cells —The cells lining the sinusoids are usually prominent in those who die during the first few days Frequently they are laden with haemosiderin granules or more commonly impregnated with non granular Prussian blue positive material (Fig 81) This haemosiderinosis is presumably the result of the considerable red cell destruction which occurs after extensive burning and is always

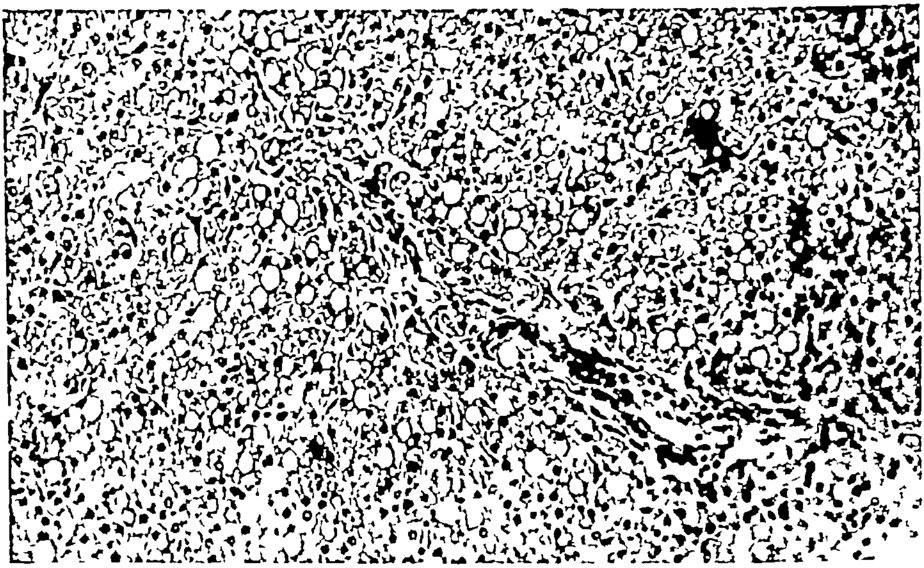


FIG 79 —Periportal fatty changes in the liver From a girl aged 3 years who died 17 days after burns on 12 per cent of her body area The fat has been dissolved out and is represented by empty spaces (Paraffin section, haematoxylin and eosin, × 140)

FIG 80 —Centrilobular fatty changes in the liver From a boy aged 4 years who died 4½ days after burns which involved 70 per cent of his body surface Heavy black indicates fat globules (Frozen section, stained oil red O, × 100)

James, Purnell and Evans (1951) studied a group of 15 patients none of whom were treated with tannic acid and found an increased urinary excretion of urobilinogen an increased retention of brom sulphthalein and abnormal thymol turbidity and cephalin-cholesterol flocculation tests in the serum Abnormalities were generally more frequent and pronounced in the more extensively burned patients In three patients studied by Wolff Elkington and Rhoads (1940) two of them treated with tannic acid the serum bilirubin levels were raised bromsulphthalein retention was increased between the fourth and fifteenth days after burning hippuric acid synthesis was im paired in two subjects, the glucose tolerance tests showed hyper glycaemic diabetic curves and there was about a 50 per cent reduc tion in the plasma prothrombin Other workers have also found a moderate reduction in plasma prothrombin activity after extensive burning (Holt, Buisseret and Vandenbroucke 1945 Levenson and his colleagues, 1946 Campbell, Gabriel and Van Hoek 1950) The plasma prothrombin was usually reduced to between 20 per cent and 50 per cent of normal activity in the 16 patients studied by Holt and his colleagues (1945) and the reduced levels lasted for weeks Restoration to normal prothrombin times was relatively slow after injections of vitamin K In burned dogs Campbell Gabriel and Van Hoek (1950) found a rapid fall of prothrombin activity in the plasma of those dying soon after burning and a slower and smaller fall in dogs which survived

Observations by anaesthetists also suggest an impairment of liver function in badly burned patients the effects of anaesthetic agents like barbiturates which are destroyed in the liver are often modified, and the dose required to produce anaesthesia is less than that required in other patients and recovery from the anaesthesia is slower

A disturbance of liver function has also been found by *in vitro* metabolic studies Evidence of an early short lived impairment of glycogenesis and a fall in the respiratory quotient were found by Clark and Rossiter (1944) in liver slices from burned rabbits and the effects were attributed to circulatory changes A significant impair ment in the rate of deamination of DL-alanine by the liver of burned rats was found by van Bekkum and Peters (1951) at the time when the urinary loss of nitrogen was high, and the impairment was probably due to an enzymatic disturbance

A disturbance in liver function might be reflected in a raised blood ammonium level Investigations on burned patients have not been reported but might help to distinguish liver failure at the biochemical level from other forms of severe burn illness Observations on extensively burned rats were made by Harkins and Long (1945) but

associated with haemosiderin deposition in the splenic pulp The sinusoidal cells are also laden and swollen with prominent fatty droplets which may give them a foamy appearance in paraffin sections. This fatty change may be present when fat is absent from the parenchymal cells Although haemosiderin accumulation and fatty change are commonly found together they are not necessarily related The meaning of the fatty change is obscure, the fat may have been phagocytosed from the bloodstream or it may be degenerative in origin

Lympholysis —Lymphoid cells are prominent in the portal tracts of patients, particularly children who die within a few hours of burning, but they are obviously fewer in most of those who die between 1 and 4 days Portal tract lymphocytes reappear in numbers about 5–8 days after injury this temporary disappearance is probably part of the general lymphonecrotic reaction since it approximates in time to the changes found in blood lymphocytes, lymph nodes and other lymphoid tissue (Chapter 16) Like these it is probably the result of adrenocortical secretion

Liver function.—Various clinico-pathological "liver function tests" have been carried out by different investigators but the interpretation of some abnormalities is rendered difficult because changes unrelated to liver dysfunction may be responsible for some of them For example hypoproteinaemia and a reversed albumin globulin ratio may result from plasma exudation into the burned skin (Chapter 10) whilst an increase in the serum bilirubin level can be related to excessive red cell destruction (Chapter 15) Other tests suggest that some degree of liver dysfunction not uncommonly develops after extensive burning but the results do not indicate a serious loss of function An increased urinary excretion of urobilin and urobilinogen is relatively common and may result from the impaired ability of the liver to excrete the excessive stercobilin formed in and absorbed from the bowel following the excessive red cell destruction A finding somewhat related to this has been noted by the author Transfusion of stored blood to some burned and injured patients may be followed by temporary jaundice, bilirubinuria and a raised serum bilirubin level, the serum giving a positive direct Van den Bergh reaction The jaundice has been shown not to be due to intravascular haemolysis from transfusion incompatibility or other causes and appears to be hepatic in origin It is known that stored blood contains about 10 per cent of non-viable red cells which rapidly disappear from the circulation and are broken down extravascularly and the post-transfusion jaundice may result from an impaired ability of the liver to excrete the extra load of bilirubin

James, Purnell and Evans (1951) studied a group of 15 patients, none of whom were treated with tannic acid and found an increased urinary excretion of urobilinogen an increased retention of brom sulphthalein and abnormal thymol turbidity and cephalin-cholesterol flocculation tests in the serum Abnormalities were generally more frequent and pronounced in the more extensively burned patients In three patients studied by Wolff Elkington and Rhoads (1940) two of them treated with tannic acid the serum bilirubin levels were raised bromsulphthalein retention was increased between the fourth and fifteenth days after burning, hippuric acid synthesis was im paired in two subjects the glucose tolerance tests showed hyper glycaemic diabetic curves and there was about a 50 per cent reduc tion in the plasma prothrombin Other workers have also found a moderate reduction in plasma prothrombin activity after extensive burning (Holt Buisseret and Vandenbroucke 1945 Levenson and his colleagues, 1946 Campbell Gabriel and Van Hoek 1950) The plasma prothrombin was usually reduced to between 20 per cent and 50 per cent of normal activity in the 16 patients studied by Holt and his colleagues (1945) and the reduced levels lasted for weeks Restoration to normal prothrombin times was relatively slow after injections of vitamin K In burned dogs Campbell Gabriel and Van Hoek (1950) found a rapid fall of prothrombin activity in the plasma of those dying soon after burning and a slower and smaller fall in dogs which survived

Observations by anaesthetists also suggest an impairment of liver function in badly burned patients the effects of anaesthetic agents like barbiturates which are destroyed in the liver are often modified and the dose required to produce anaesthesia is less than that required in other patients and recovery from the anaesthesia is slower

A disturbance of liver function has also been found by *in vitro* metabolic studies Evidence of an early short-lived impairment of glycogenesis and a fall in the respiratory quotient were found by Clark and Rossiter (1944) in liver slices from burned rabbits and the effects were attributed to circulatory changes A significant impair ment in the rate of deamination of DL alanine by the liver of burned rats was found by van Bekkum and Peters (1951) at the time when the urinary loss of nitrogen was high, and the impairment was probably due to an enzymatic disturbance

A disturbance in liver function might be reflected in a raised blood ammonium level Investigations on burned patients have not been reported but might help to distinguish liver failure at the biochemical level from other forms of severe burn illness Observations on extensively burned rats were made by Harkins and Long (1945) but

were confined to the first 12 hours after injury The blood ammonia-nitrogen was definitely increased and was associated with a raised liver amino-nitrogen and a slightly increased liver ammonia-nitrogen, all of which could result from impaired liver activity

Severe burning seems to have no effect on the rate of regeneration of liver substance after hepatectomy Desmarais (1949) subjected rats to a standard partial (65 per cent) hepatectomy and a few hours later burned half of them The rate of liver regeneration in the burned and unburned animals was similar during the next few days, and 5 days after burning the regeneration was just as complete (85 per cent) in both sets of animals

Pathogenesis.—The acute onset of a moderate degree of liver dysfunction may often result from hepatic hypoxia of circulatory origin During the shock phase the development of oligaemia is followed by a reduced cardiac output and considerable constriction of arteries and veins (Chapter 9) The circulation through organs and tissues not immediately essential for survival is considerably reduced in order to maintain the blood flow through the heart and brain and there is evidence that the hepatic blood flow after burning may be considerably reduced The circulation through the liver of burned dogs was studied by Dobson and Warner (1954) using the rate of disappearance of intravenously injected radioactive chromic phosphate, the colloid form of which is removed by the liver Hepatic circulation was slowed within minutes of burning and was further retarded as shock developed The progressive slowing of the blood flow through the mesentery of scalded dogs or cats reported by Abell and Page (1943) indicates that the splanchnic and therefore the portal circulation is greatly reduced after burning Hepatic ischaemia may be followed by hypoxia, and since most of the blood supply to the liver is venous the liver cells may readily suffer from further reduction of oxygen On the other hand the slight and infrequent liver-cell necrosis in fatally burned untanned subjects suggests that the liver cells at the morphological level are relatively resistant to hypoxia even though metabolic and biochemical disturbances may occur There is also evidence of hepatic hypoxia in traumatic and haemorrhagic shock For example in experimental animals Engel (1945–46) found that the oxygen saturation of the blood, first in the hepatic vein and then in the portal vein, fell during haemorrhage He also found a reduced *in vitro* oxygen consumption of liver slices from animals in haemorrhagic or traumatic shock which indicated a disturbance of cell oxidative metabolism After burning, however, the oxygen uptake of liver slices from rats is unimpaired (Clark and Rossiter, 1944, Harkins and Long, 1945)

Continued liver dysfunction or its later development may result from a variety of causes of which bacterial toxaemia and invasion of micro-organisms from the infected skin may be the most important It might also be related to the loss of flesh and the katabolic response of the patient as envisaged by Monsaingeon (1952) Silent incompatible blood transfusion reactions may occasionally be responsible and hepato-toxic agents like sulphonamides and aureomycin may sometimes play a part as well as subicteric virus hepatitis from plasma or blood transfusion

PLASMA JAUNDICE

A virus hepatitis may develop between 6 weeks and 6 months after transfusion of plasma or whole blood It results from the transfer of the virus SH the activity of which is preserved even when the plasma is dried In burned patients plasma is the more frequent offender because of the large volumes administered and because a single batch is pooled from a number of donors The disease is believed to be transmitted by a blood donor carrying the virus in his blood Normally virus hepatitis is a mild disease but it may run a more dangerous course in patients already ill with unhealed burns and possibly an already damaged liver Jaundice may appear either while the patients are still in hospital or weeks or months after discharge Jaundice has also developed in patients re admitted for plastic surgery The incidence of virus hepatitis is difficult to determine because of the long incubation period and frequency of subclinical types The report to the Ministry of Health (1954) gives the incidence of jaundice following whole blood transfusion as 0 16 per cent, following dried "small pool" plasma as 0 12 per cent and following dried large pool plasma as 4 per cent Lehane and his colleagues (1949) reported figures 3–10 times as frequent

Unfortunately there is no way of inactivating the virus in the plasma so that the risk of jaundice can be reduced only (1) at the processing level by reducing the number of donors in each plasma pool to 10 or less per batch (2) at the transfusion level by giving each patient plasma from the least number of batches possible and preferably from only one batch and (3) by adequate *heat* sterilization of all syringes needles and instruments

The pathology and clinical features of the disease are well described by Sherlock (1955)

THE GALL BLADDER

Not infrequently autopsy of a burned jaundice free child reveals a gall bladder distended with a clear watery bile free fluid The hepatic and common bile ducts communicate normally and contain

unconcentrated liver bile Compression of the bladder results in a flow of the watery fluid through the ampulla of Vater The aetiology of this *mucocele* or *hydrocele* is uncertain it might result from external compression of the cystic duct from swollen lymph nodes in the gastro-hepatic omentum since these are usually enlarged and hyperaemic like most other lymph nodes in fatally burned children The absence of obstruction to the hepatic and common bile ducts does not support this view whilst the fact that compression of the bladder readily produces a flow of fluid suggests that *in vivo* constriction of the smooth muscle in the cystic duct was probably responsible

REFERENCES

Abell, R G, and Page, I H (1943) *Surg Gynec Obstet*, **77**, 348
Baker R D (1945) *Amer J Path* **21**, 717
Bardeen, C R (1897) *Johns Hopk Hosp Rep*, **7**, 137
Barnes J M, and Rossiter, R J (1943) *Lancet* **2**, 218
van Bekkum, D W, and Peters, R A (1951) *Quart J exp Physiol*, **36**, 127
Belt, T H (1939) *J Path Bact*, **48**, 493
Buis, L J, and Hartman, F W (1941) *Amer J Clin Path*, **11**, 275
Cameron, G R, Milton R F, and Allen J W (1943) *Lancet*, **2**, 179
Campbell, D A, Gabriel, L T, and Van Hoek, D E (1950) *Surg Forum, Amer Coll Surg*, 515
Clark, E J, and Rossiter, R J (1943) *Lancet*, **2**, 222
— — (1944) *Quart J exp Physiol*, **32**, 269
Davidson, E C (1925) *Surg Gynec Obstet*, **41**, 202
Desmarais, A (1949) *Laval Medical*, **14**, 346
Dobson, E L, and Warner, G F (1954) *Fed Proc*, **13**, 36
Dunbar, J (1934) *Glasg med J*, **122**, 239
Engel, F L (1945–46) *J Mt Sinai Hosp*, **12**, 152
Erb, I H, Morgan, E M, and Farmer, A W (1943) *Ann Surg*, **117**, 234
Gibson, T (1945) In *Studies on Burns and Scalds*, p 192 M R C Special Report Series No 249
Gillman, J, and Gillman, T (1948) *S Afr J med Sci*, **13**, 169
Harkins, H N, and Long, C N H (1945) *Amer J Physiol*, **144**, 661
Hartman, F W, and Romence, H L (1943) *Ann Surg*, **118**, 402
Holt, J P, Buisseret, J, and Vandenbroucke, J (1945) *C R Soc Biol*, **139**, 86
Jackson, A W (1944) *Med J Aust*, **2**, 352
James, G W, Purnell, O J, and Evans, E I (1951) *J clin Invest*, **30**, 191
Lehane, D, Kwantes, C M S, Upward, M G, and Thomson, D R. (1949) *Brit med J*, **2**, 572
Levenson, S M, Adams, M A, Green, R W, Lund, C C, and Taylor, F H L (1946) *New Engl J Med*, **235**, 467
Ministry of Health, Medical Research Council and Department of Health Scotland, Report to (1954) *Lancet*, **1**, 1328
Monsaingeon, A (1952) *Mem Acad Chir*, **6**, **7**, 197
Olbrycht, J (1924) *Rev Medicine*, **41**, 81
Rae, S L, and Wilkinson, A W (1944) *Lancet*, **1**, 332
Sherlock, S (1955) *Diseases of Liver and Biliary System* Oxford, Blackwell
Weiskotten, H G (1919) *J Amer med Ass*, **72**, 259
Wells, D B, Humphrey, H D, and Coll, J J (1942) *New Engl J Med*, **226**, 629
Wilson, W C (1942) *Report to the War Office and Medical Research Council* Quoted by Barnes and Rossiter (1943)
— Macgregor, A R, and Stewart, C P (1938) *Brit J Surg*, **25**, 826
Wolff, W A, Elkington, J R, and Rhoads, J E (1940) *Ann Surg*, **112**, 158
Zinck, K. H (1940) *Klin Wschr*, **19**, 78

CHAPTER 23

SPECIAL KINDS OF BURNS—FLASH AND RADIATION BURNS

CERTAIN burns of the skin differ from the familiar burns and scalds and require special consideration Flash burns atomic bomb burns and burns from x radiation and radium are discussed in this chapter electric burns and chemical burns are considered in Chapter 24

FLASH BURNS

Flash burns may be defined as burns caused by exposure to a high intensity of heat for a brief interval They may result from conduction convection or radiation of thermal energy Burns from contact of the skin with a red hot poker for a fraction of a second or from a short blast of very hot air are flash burns For example exposure of the skin to a blast of air at 300°–500°C for less than 1 second causes erythema and blistering of the skin (Ashe and Roberts 1945)

However the term is generally restricted to burns produced by a flash of intense *radiant* energy and further consideration will be confined to this type Such burns have been known to underground miners for centuries—during an explosion a flash of flame may burn victims nearby In warfare flash burns first came into prominence during the incendiary bomb attack on Pearl Harbour but they were particularly important after the atomic bomb explosions over Hiroshima and Nagasaki when the flash burned victims were numbered in tens of thousands

THE BURNED SKIN

The tissue changes and the inflammatory reaction produced by flash burns are essentially the same as those which follow ordinary burns and scalds Burns of all degrees of severity can be produced varying from very superficial burns showing little alteration of the epidermis to heat-coagulated (Fig 82) or even charred injuries involving the whole thickness of the skin Experimental burns which followed brief exposure of pigs to intense radiant heat flash were studied by Pearse Payne and Hogg (1949) and Hogg Payne and Pearse (1950) Mild, moderate and severe burns followed magnesium flash (3 700 C flash time 0 34 second) the severity increasing as the distance from

the flash decreased from 60 to 20 centimetres Histologically the burns were said to be characterized by an abrupt demarcation at the edge between normal and abnormal skin and also at a horizontal level within the skin At the margin there was a sharp transition from the unburned basiphilic epidermis to eosinophilic heat-coagulated epithelium showing nuclear pyknosis and other cytological changes, and a similar abrupt demarcation from heat coagulation to almost normal appearance was said to have been present in the hair follicles This effect is consistent with theory since it can be argued that the brief exposure to a high energy source might burn the surface layers but not permit penetration of heat to the deeper layers of the skin (Chapter 1) Nevertheless the skin deep to the coagulated surface developed a considerable inflammatory reaction with much oedema and a polymorphonuclear leucocyte migration, which suggests that heat did penetrate below the coagulated surface Similarly the infra-red flash burns reported by Butterfield produced an inflammatory reaction, with intense vasodilatation, blistering and subcutaneous oedema (Butterfield, 1951, Butterfield and his colleagues, 1956) On the other hand the acute inflammation might have resulted from a chemical substance like leukotaxine released from heat-damaged tissue and acting on vessels in the deeper tissues (*see* Chapter 3) In practice the development of oedema in flash burns means that extensively flash-burned patients will require plasma transfusion to maintain the blood volume just like other patients with large burns

TRANSFER AND UPTAKE OF HEAT

Because radiant energy travels in straight lines the area burned always faces the source of heat The opposite side of the limb or body is protected because it is in shadow

The severity of burning depends largely on the uptake of incident energy per unit area of skin because the burning period is very brief Energy uptake increases with (1) the temperature of the heat source and (2) the duration of exposure, and decreases with (3) increasing distance between the victim and the heat flash

Calorie uptake and severity of burning—The amounts of energy falling on the skin in a brief interval which just produce burns of different degrees of severity were investigated by Butterfield (1951), Morton, Kingsley and Pearse (1952) and Butterfield and his colleagues (1956) The results varied somewhat with different sources of heat and the lowest thresholds were found when infra-red radiation was greatest In Butterfield's experiments the arms of volunteers were exposed behind a time-shutter either to a gas-fired radiant panel

heated to 1 000°C and emitting mostly infra red radiation or to a carbon arc source of white heat emitting about 20 per cent of its energy in the infra red With predominant infra red radiation absorption of about 1 calorie per square centimetre (cal /cm ^{2}) of skin within 1 second produced a temporary erythema whilst blister burning resulted when the dose exceeded 1 8–2 3 cal /cm ^{2} The thresholds for the white-hot source were higher 2 0 cal /cm ^{2} resulted in erythema, 3 5 cal /cm ^{2} in shallow blistering, 4 8 cal /cm ^{2} in deep blistering and 5 2 cal /cm ^{2} in full thickness skin loss burns The thresholds found by Morton Kingsley and Pearse (1952) were somewhat higher They exposed the flanks of white skinned pigs to the concentrated beam of a carbon arc searchlight emitting 35 per cent of its energy in the infra red part of the spectrum and the heat taken up by the skin was varied by varying the source energy emission Absorption of 3 cal /cm ^{2} produced an erythematous burn 5 5 cal /cm ^{2} just produced a patchily coagulated burn and 8 5 cal /cm ^{2} was followed by complete surface coagulation

Effect of clothing.—The depth of burning may be affected by the fraction of incident energy reflected by clothing Uncovered skin generally absorbs more radiant energy than clothed skin and suffers worst from flash burns unless the incident energy is so large that it matters little if a fraction is reflected by a covering fabric In Hiroshima, clothing, particularly white clothing which reflects radiant energy sometimes prevented superficial or moderately severe flash burns but the victims were then situated in the periphery of the city Clothing did not protect those exposed to skin-charring or coagulating flash in the central area.

In experimental flash burns the protection offered by clothing varied with different fabrics and many gave little protection (Morton Kingsley and Pearse, 1952) The extra energy required to burn skin behind the fabric varied from zero with a black undershirting material to 4 5 cal /cm ^{2} with a similar material white in colour Other fabrics such as silk sateen linen serge and twill gave intermediate results White or pale-coloured cloths gave better protection than black or dark-coloured ones and for example raised the threshold for certain burns from 5 5 to 10 0 cal cm ^{2} The protection given by 2 or more layers of cloth was not necessarily cumulative and combinations of certain fabrics offered less protection than a single layer of another material

Severe burns were often produced even though the cloth was not damaged because more energy is required to injure most fabrics than to coagulate skin

ATOMIC BOMB BURNS

Burns from atomic bomb explosions cannot be considered adequately without discussing the main causes and effects of "atomic bomb disease" experienced by the unfortunate Japanese The present account is based on the Japanese Medical Report on Atomic Bomb Effects (Tsuzuki and his colleagues, 1953), on the findings and data communicated by medical and biophysical scientists to the International Medical Commission on the Effects on Human Health of Atomic and Hydrogen Bombs (Chevallier and his colleagues, 1955) and on other reports (Effects of Atomic Weapons, 1950, Kusano, 1953)

The atomic bombs which were dropped in August 1945 exploded at a height of 500–600 metres, and destroyed most of Hiroshima and an extensive area of Nagasaki Material destruction was caused by the terrific air blast and the raging fires following the intense heat flash Two to three hundred thousand people died, many instantaneously, most within a few days or weeks, but the full toll has not yet been taken The delayed results of exposure to radiation—leukaemia and aplastic anaemia—are still claiming victims In Nagasaki, Hayashi (1955) reported that the incidence of congenitally malformed babies among the stillbirths born to survivors up to 1953 was much greater than the incidence among the stillbirths born to non-exposed parents during the same period This was interpreted as evidence of genetic damage caused by exposure to the exploding bomb (Sevitt, 1955)

Injury and death from the explosions resulted from one or more of the following causes (1) *Burns*, mainly from heat flash but also from scorching and ignition of clothing and from secondary fires (2) *Trauma*, caused by collapsing structures, flying glass splinters and air blast (3) *Radioactivity*, from the exploding bomb

HEAT FLASH AND BURNS

The temperature of the exploding fireball momentarily reached 1 million degrees Centigrade, comparable to that of the sun, and an intense flash of heat was radiated in all directions The ground surface directly beneath (the hypocentre) was transiently heated to 3,000°–6,000°C and the Civil Engineering Survey in Japan concluded that a heat wave at 2,000°C extended more than 600 metres from the hypocentre In the central area the surface of granite and roof tiles were melted and wooden buildings were ignited within 3 kilometres

There were tens of thousands of casualties from flash burns and thousands more from flame burns, ignition of clothing often increasing the extent of burning In Hiroshima the severity of the flash

burns varied mainly with the distance from the bomb in those directly exposed. Those within 1 5 kilometres of the hypocentre were fatally burned, often instantaneously charred and many victims were stripped of their burned skin by the blast which followed Those exposed within 3 kilometres received deep coagulated burns, but farther out the burns were less severe and were generally superficial in those more than 4 kilometres from the hypocentre About three quarters of all the casualties were burned about 30 per cent of the fatal casualties were due to flash burns and more than half due to flash and flame

FIG 82.—Flash burn at Hiroshima. (Haematoxylin and eosin × 120) (*Section by courtesy of Dr N Kusano Tokyo*)

Most of the people were lightly clad but clothing offered little protection except to those in the outer ring of the cities who were flash burned only on exposed areas The flash burned skin always faced the fireball

It has been calculated that at 1 4 kilometres from the hypocentre the heat uptake from the explosion of a "nominal" atomic bomb is 20 cal /cm² at 2 3 kilometres it is 7 cal cm²—more than sufficient to produce a whole skin loss burn (*vide supra*)—and at 4 kilometres it is 2 5 cal /cm² which is about the threshold for erythematous burns (Brooks and his colleagues 1952) Butterfield (1951) calculated that the deep and superficial burning respectively would occur in a somewhat wider range

Infra red radiation was probably responsible for the major burning effect and the contribution of ultra violet radiation appears to have been of minor importance

RADIOACTIVE BOMBARDMENT

The flash of the fireball was associated with and followed by a radioactive emission, mainly of neutrons and gamma rays but also of alpha and beta particles The ionizing radiation induced some radioactivity in the earth and buildings which persisted for some days, but local "fall-out" of radioactive fission products appears to have been limited because the upward reflection from the ground of the down blast carried particulate matter high into the atmosphere Some fell in a suburb of Nagasaki and elsewhere and produced pathological effects

The zone of radioactive bombardment within which acute radiation disease occurred was smaller than the area of effective flash burning, but many persons within buildings and sheltered from the heat flash received a considerable intensity of radiation on their bodies because of the penetrating power of neutrons and gamma-rays The intensity of gamma-radiation was so large (more than 10,000 r) within 0 7 kilometre as to have been rapidly fatal, at 1 2 kilometres it was 1,000 r, at 1 4 kilometres it was 400 r (the 50 per cent lethal dose), at 1 7 kilometres it was 100 r and beyond this it fell off to between 10–30 r at 2 3 kilometres Fast neutron bombardment was additional but its lethal effect was mainly concentrated in the fatal gamma-ray zone

Therefore many flash-burned victims in the ring about 1 5–3 kilometres from the hypocentre must have received a "mild" or "subclinical" dose of radiation (*vide infra*)

Acute radiation disease—Clinically, in fully developed cases prodromal symptoms of fever, lassitude, anorexia and diarrhoea were followed by a latent period Then haemorrhagic symptoms, petechiae, melaena, haematuria and haematemesis occurred, stomatitis, gingivitis, pharyngitis, which were often necrotic, appeared as well as bloody diarrhoea from intestinal ulceration If the patient survived, epilation commenced in the second or third week Rapidly fatal cases died before haemorrhagic or ulcerative changes developed, but in those mildly affected, symptoms were often confined to epilation or bleeding and in some patients only leucopenia was demonstrated Recovery was usually very slow, taking months in the majority of cases

The frequency and severity of radiation disease depended on the amount of radiation received and was largely related to the distance of the inhabitants from the point of the explosion and on their degree of shelter by solid buildings The clinical picture developed in about 80 per cent of the hospitalized casualties located within

1 kilometre of the ground centre at the time of the explosion in 14–34 per cent of those between 1 and 2 kilometres and in 4–9 per cent of those between 2 and 2 8 kilometres Those within 1 kilometre nearly all died, moderate or severe disease developed in those at 1–2 kilometres and the acute effects were slight in those farther away The over all death rate was very high and most of the deaths occurred within 2 or 3 weeks of the bombing

Pathologically radiation disease was characterized by destruc tion or degeneration of lymphatic tissue and the haemopoietic system, by ulceration of mucous membranes and by subsequent bacterial invasion of the blood stream, lungs and other organs The peripheral blood showed thrombocytopenia, agranulocytosis or neutropenia lymphopenia and anaemia Degenerative changes occurred in the alimentary tract testes or ovaries, skin pituitary adrenals and other organs

BURNING AND RADIATION COMBINED

Patients extensively burned and with overt radiation disease had a very high mortality but there were also many relatively slightly burned patients who died Some of these had mild symptoms of radiation disease but many had not No doubt lack of plasma and other medical supplies malnutrition and infection contributed to the deaths of many burned patients but the mortality from relatively slight burns was so high that it was probable that another factor was involved Many burned patients without symptoms of radiation disease were found to have leucopenia instead of the expected leucocytosis This raises the possibility that mild or subclinical radiation effects had augmented the severity of the burn illness and increased the fatality rate

Experimental investigations have shown that the combination of small or moderately extensive burns with subclinical irradiation results in a considerable mortality rate In dogs, Brooks and his col leagues (1952) inflicted burns on 20 per cent of the body surface com bined with doses of either 25 r or 100 r total body x radiation Twelve per cent died in the burned only group 20 per cent died among the burned + 25 r" animals 73 per cent among the "burned + 100 r animals whilst there were no deaths among the irradiated but unburned dogs The leucocyte count was only slightly reduced in the irradiated only group but a considerable leucopenia occurred in the burned + 100 r animals most of which developed a fatal septicaemia through the invasion of haemolytic streptococci from the burned skin Similar results were reported by Korlof (1956) who inflicted small burns on the backs of guinea pigs (1–1 5 per cent

of the body area) and investigated the effect of 250 r radiation Only 9 per cent of the "burned only" and 10 per cent of the "irradiated only" animals died, but the fatality rate was 38 per cent among those burned and irradiated Bacteriological studies showed that various bacteria were invading the blood stream from the burned area on the irradiated animals Leucopenia was found and few leucocytes were seen in the burned, granulating skin

It may be concluded that a small or moderate burn of little importance by itself becomes a serious injury when it is combined with a subclinical or a moderate dose of whole-body radiation, partly because of bacterial invasion from the burn and partly because of a leucopenia and lack of leucocyte response in the burned skin Humoral immunity may also be affected

BURNS FROM X-RAYS AND RADIOACTIVE SUBSTANCES

Skin burns from radium and x-radiation have been a not infrequent occupational hazard among radiologists and others They are characterized by a delayed appearance, pain, persistence, slow—often repeated—sloughing, slow healing, dense scarring and a later inclination to malignant change

PHYSICAL AND PATHOLOGICAL PRINCIPLES

The power to produce local changes is a property of the rays and particles which are absorbed by the skin but not of those which pass through unchanged Absorption by cells produces ionizing and electrolytic effects in the nuclei and cytoplasm with consequent damage X-rays, gamma rays and beta particles expend their energy by the ejection of high-speed electrons Irradiation has a local cumulative effect lesions in the skin may be caused by one large dose or by a series of small, repeated doses each of which has no clinical effect if given alone

Radium.—The effects of radium on the skin are mainly the result of alpha and beta particles and the less rapid, less penetrating beta particles are especially important These particles penetrate poorly, are absorbed by the skin and inflict damage at a relatively low dosage

X-radiation.—The destructive power of x-rays is directly proportional to their wavelength and inversely proportional to their frequency Low frequency or soft rays penetrate less readily than high frequency, hard rays (gamma rays), they are more readily absorbed by the skin and have a greater destructive power Hard x-rays require a dosage as high as 1,000–2,000 r to burn the skin Hardness

increases with voltage and filtration and is influenced by the size of the field The surface intensity also increases with voltage and decreases with the square of the distance between the tube and the target

Action and effects on cells.—It is agreed that alpha beta and gamma rays and x radiation produce more or less similar effects although their efficiency varies

Degeneration and necrosis of the skin is produced by one or both of two mechanisms (1) direct action on cells (2) indirect ischaemic effects from thrombosis and sclerosis of blood vessels

Direct cellular action—This appears to depend on the degree and localization of intracellular ionization produced by the absorbed radiations and may result either from a direct hit or from the physico-chemical action of the decomposition products of intra cellular water The changes include coagulation of proteins destruc tion of sulphydryl groups liberation of histamine hydrogen peroxide atomic hydrogen and OH radicles Cameron (1952) recognizes three stages of radiation injury in most somatic cells (1) alteration of cell formation (2) alteration of structure, and (3) necrosis From the experimental evidence produced it is doubtful whether radiation exerts any *direct* action on intracellular respiratory or glycolytic enzymes

The primary action is on the nucleus and on the processes of growth. Chromatin is affected particularly in cells undergoing mitosis chromosomes are broken abnormal mitoses are produced and the division is altered or arrested The earliest nuclear effects are vacuolation and increase of size Alterations in cytoplasm result from a disturbance in its colloid state In some cells the protoplasm becomes turbid finely granular and eventually coarsely granular These changes may lead to the death or modified function of the cells or their offspring Intercellular substances especially collagen and elastica are also affected

SKIN LESIONS

The changes produced by alpha and beta particles and by soft x rays look identical The initial response to hard x rays is also similar but because these penetrate more deeply and are absorbed by deeper cells the zone of destruction is deeper and subsequent scarring is more severe There are regional differences in susceptibility for example the skin over the sternum back of the hand and front of the tibia are said to be less tolerant than other areas Hair follicles sweat glands the nail bed and blood vessels are particularly susceptible

The lesions may be classified into (1) *acute burns*, due to one or more large doses, and (2) *chronic dermatitis* due to repeated small doses over a long period

Acute burns—Surface changes are absent for the first few days after exposure but intracellular effects occur almost immediately The first visible sign of burning is erythema 4–10 days later The severity or depth of burning varies considerably and may be classified into (1) superficial and (2) deep burns

(1) With minimal burning the erythema subsides in a few days and is followed by local epilation within 2 or 3 weeks In other burns the erythema is more prolonged, the superficial dermis desquamates, the hairs fall out and the skin becomes pigmented Epilation is permanent and the skin is dry because the follicles and sweat coils are destroyed

(2) In more severe burns the erythema is intense and is accompanied by persistent severe pain which lasts for weeks Blisters appear about 2 weeks after exposure and the skin becomes necrotic later Healing is slow and eventually a permanently hairless scar is produced In the deepest burns the process is similar but the necrosis and sloughing involve the subcutaneous tissues, possibly the fascia and muscle and a deep painful ulcer forms This is resistant to therapy and heals very slowly The end result is a dense subcutaneous fibrosis covered by a thin unstable epithelium

The healed scars have a tendency to break down in later years and the chronic ulcers tend to become malignant

Chronic dermatitis.—This is characterized by skin atrophy, hyperkeratosis, telangiectasis and multiple small ulcers

Histological changes—In the acute stage, the epidermis shows a degeneration of the Malpighian layer with disintegrative necrosis and nuclear lysis and karyorrhexis of many cells The hair follicles, sweat ducts and coils are similarly affected The dermal vessels are greatly dilated and congested, oedema is present, and there is an infiltration of leucocytes which are often concentrated around the blood vessels and hair follicles The collagen fibres are altered and swollen Vascular endothelium is also swollen or necrotic, small haemorrhages are present and some of the blood vessels are thrombosed Tissue necrosis may follow and an obliterating endarteritis may be seen

In severe chronic lesions the epithelial cell nuclei are also damaged and the hair follicles, sweat glands and sebaceous glands atrophy and disappear Epithelial regeneration is poor The dermal collagen

becomes thick sclerotic and hyaline Blood vessels are damaged, some are thrombosed, others are narrowed by an obliterating endarteritis some of the dermal vessels later become telangiectatic

Effects of atomic and hydrogen bomb explosions.—In Hiroshima and Nagasaki radiation burns were not seen because there the whole body was irradiated Those exposed for a short period to an intensity of radiation sufficient to produce burning developed a fulminating

FIG. 83—Alopecia from a radiation burn of the scalp due to surface contact by radioactive dust Fisherman aboard the *Fukuryu Maru* which was showered with radioactive dust after an H-bomb explosion at Bikini in 1954 (*By courtesy of Dr K. Miyoshi Tokyo*)

radiation disease and died before burns could develop (*vide supra*) Epilation was a characteristic of radiation disease but it involved most of the body hair was a temporary phenomenon and was not associated with other changes seen in local radiation burns

On the other hand after one of the hydrogen bomb explosions at Bikini in 1954 the heavy fall-out of radioactive fission products on the fishing boat, the *Fukuryu Maru* located 90–100 miles from the explosion did produce local radiation dermatitis in the fishermen (Fig 83) as well as systemic radiation disease (Sevitt, 1956a and b) This was because parts of the skin (scalp waistline armpits groins)

The lesions may be classified into (1) *acute burns*, due to one or more large doses, and (2) *chronic dermatitis* due to repeated small doses over a long period

Acute burns.—Surface changes are absent for the first few days after exposure but intracellular effects occur almost immediately The first visible sign of burning is erythema 4–10 days later The severity or depth of burning varies considerably and may be classified into (1) superficial and (2) deep burns

(1) With minimal burning the erythema subsides in a few days and is followed by local epilation within 2 or 3 weeks In other burns the erythema is more prolonged, the superficial dermis desquamates, the hairs fall out and the skin becomes pigmented Epilation is permanent and the skin is dry because the follicles and sweat coils are destroyed

(2) In more severe burns the erythema is intense and is accompanied by persistent severe pain which lasts for weeks Blisters appear about 2 weeks after exposure and the skin becomes necrotic later Healing is slow and eventually a permanently hairless scar is produced In the deepest burns the process is similar but the necrosis and sloughing involve the subcutaneous tissues, possibly the fascia and muscle and a deep painful ulcer forms This is resistant to therapy and heals very slowly The end result is a dense subcutaneous fibrosis covered by a thin unstable epithelium

The healed scars have a tendency to break down in later years and the chronic ulcers tend to become malignant

Chronic dermatitis—This is characterized by skin atrophy, hyperkeratosis, telangiectasis and multiple small ulcers

Histological changes—In the acute stage, the epidermis shows a degeneration of the Malpighian layer with disintegrative necrosis and nuclear lysis and karyorrhexis of many cells The hair follicles, sweat ducts and coils are similarly affected The dermal vessels are greatly dilated and congested, oedema is present, and there is an infiltration of leucocytes which are often concentrated around the blood vessels and hair follicles The collagen fibres are altered and swollen Vascular endothelium is also swollen or necrotic, small haemorrhages are present and some of the blood vessels are thrombosed Tissue necrosis may follow and an obliterating endarteritis may be seen

In severe chronic lesions the epithelial cell nuclei are also damaged and the hair follicles sweat glands and sebaceous glands atrophy and disappear Epithelial regeneration is poor The dermal collagen

becomes thick, sclerotic and hyaline Blood vessels are damaged some are thrombosed, others are narrowed by an obliterating endarteritis some of the dermal vessels later become telangiectatic

Effects of atomic and hydrogen bomb explosions.—In Hiroshima and Nagasaki radiation burns were not seen because there the whole body was irradiated Those exposed for a short period to an intensity of radiation sufficient to produce burning developed a fulminating

FIG 83 —Alopecia from a radiation burn of the scalp due to surface contact by radioactive dust Fisherman aboard the *Fukuryu Maru* which was showered with radioactive dust after an H-bomb explosion at Bikini in 1954 (*By courtesy of Dr K Miyoshi Tokyo*)

radiation disease and died before burns could develop (*vide supra*) Epilation was a characteristic of radiation disease but it involved most of the body hair was a temporary phenomenon and was not associated with other changes seen in local radiation burns

On the other hand after one of the hydrogen bomb explosions at Bikini in 1954 the heavy fall-out of radioactive fission products on the fishing boat, the *Fukuryu Maru* located 90–100 miles from the explosion did produce local radiation dermatitis in the fishermen (Fig. 83) as well as systemic radiation disease (Sevitt 1956a and b) This was because parts of the skin (scalp waistline armpits groins)

were in prolonged contact with the radioactive dust The skin became acutely inflamed, the hair fell out permanently and eventually the healed areas were depigmented or more pigmented than usual

REFERENCES

Ashe, W F, and Roberts, L B (1945) *War Med*, **7**, 82

Brooks, J W, Evans, E I, Ham, W T, and Reid, J D (1952) *Ann Surg*, **136**, 533

Butterfield, W J H (1951) In *Symposium on Burns*, p 23 National Research Council, Washington

Butterfield, W J H, Seager, E R D, Dixey, J R B, and Treadwell, E E (1956) *Surg Gynec Obstet*, **103**, 655

Cameron, G R (1952) *Pathology of the Cell* Edinburgh and London, Oliver & Boyd

Chevallier, P, Gale, G W, Gietzelt, F, Guzman, L, Holubec, K, Kozlova, A, Pai Hsi Ching, Sevitt, S, and Voncken, J (1955) *Preliminary Report of the International Medical Commission on the Effects on Human Health of Atomic and Hydrogen Bomb Explosions*

Effects of Atomic Weapons (1950) U S Atomic Energy Commission, New York

Hayashi, I (1955) *Report to the International Medical Commission on the Effects on Human Health of A and H-bomb Explosions*

Hogg, L, Payne, J T, and Pearse, H E (1950) *Arch Path*, **50**, 267

Korlof, B (1956) *Acta chir scand* suppl, **209**, 117

Kusano, B (1953) *Atomic Bomb Injuries* Tokyo [in English]

Morton, J H, Kingsley, H D, and Pearse, H E (1952) *Surg Gynec Obstet*, **94**, 317, 497

Pearse, H E, Payne, J T, and Hogg, L (1949) *Ann Surg*, **130**, 774

Sevitt, S (1955) *Lancet*, **2**, 199

— (1956a) *Med World*, **84**, 385

— (1956b) *Conditions de vie et la sante*, Vol **1**, p 37

Tsuzuki, M, Sassa, K, Nakaidzumi, M, Kinoshita, R, and Miyake, M (1953) *Medical Report on Atomic Bomb Effects, National Research Council, Japan, Tokyo* [in English]

CHAPTER 24

SPECIAL KINDS OF BURNS—ELECTRICAL AND CHEMICAL BURNS

ELECTRIC BURNS AND SHOCK

AMONG the first to study the biological effects of electricity was the French revolutionary Marat, who discharged Leyden jars on hens and goats After the introduction of dynamo generators a stage hand was killed at Lyons in 1879 and a year later a man was electrocuted near Birmingham (Jex Blake, 1913)

Nowadays in Britain 120–150 people are killed in electrical accidents each year but the total number of accidents is impossible to determine About 5 per cent of electrical accidents in factories are fatal and nearly half of these are at tensions below 250 volts and a minority are at high tensions (Report of the Chief Inspector of Factories, 1954) The conditions under which fatal accidents happen differ little from those responsible for minor accidents and it follows that many of the latter might easily be very serious About 40 per cent of factory accidents are due to portable electrical tools and handlamps and their connexions The Factory Inspectorate strongly recommends a reduction in tension to 110 volts or less for portable instruments and to 25 volts for handlamps and Emerson (1956) estimates that if this were universally adopted the number of fatalities from electrical accidents at work would be halved. In Canada Gaby (1927) reported that 90 per cent of electrical injuries were burns

The hazards from the use of electricity are (1) electric burns (2) electric shock, (3) fire and explosion and (4) eyeflash chiefly from arc welding

Electric burns and shock will be considered here True electric burns and shock are caused by contact of the skin with a conductor of electricity when the circuit is complete Part of the body must be interposed between two conductors one of which may be the ground

ELECTRIC BURNS

Some confusion has arisen through differences in nomenclature because there are two main kinds of electric burns Some workers consider the true electric lesion to be different from a burn (for

were in prolonged contact with the radioactive dust The skin became acutely inflamed, the hair fell out permanently and eventually the healed areas were depigmented or more pigmented than usual

REFERENCES

Ashe, W F, and Roberts, L B (1945) *War Med*, **7**, 82
Brooks, J W, Evans, E I, Ham, W T, and Reid, J D (1952) *Ann Surg*, **136**, 533
Butterfield, W J H (1951) In *Symposium on Burns*, p 23 National Research Council, Washington
Butterfield, W J H, Seager, E R D, Dixey, J R B, and Treadwell, E E (1956) *Surg Gynec Obstet*, **103**, 655
Cameron, G R (1952) *Pathology of the Cell* Edinburgh and London, Oliver & Boyd
Chevallier, P, Gale, G W, Gietzelt, F, Guzman, L, Holubec, K, Kozlova, A, Pai Hsi Ching, Sevitt, S, and Voncken, J (1955) *Preliminary Report of the International Medical Commission on the Effects on Human Health of Atomic and Hydrogen Bomb Explosions*
Effects of Atomic Weapons (1950) U S Atomic Energy Commission, New York
Hayashi, I (1955) *Report to the International Medical Commission on the Effects on Human Health of A and H-bomb Explosions*
Hogg, L, Payne, J T, and Pearse, H E (1950) *Arch Path*, **50**, 267
Korlof, B (1956) *Acta chir scand* suppl, **209**, 117
Kusano, B (1953) *Atomic Bomb Injuries* Tokyo [in English]
Morton, J H, Kingsley, H D, and Pearse, H E (1952) *Surg Gynec Obstet*, **94**, 317, 497
Pearse, H E, Payne, J T, and Hogg, L (1949) *Ann Surg*, **130**, 774
Sevitt, S (1955) *Lancet*, **2**, 199
— (1956a) *Med World*, **84**, 385
— (1956b) *Conditions de vie et la sante*, Vol **1**, p 37
Tsuzuki, M, Sassa, K, Nakaidzumi, M, Kinoshita, R, and Miyake, M (1953) *Medical Report on Atomic Bomb Effects, National Research Council, Japan, Tokyo* [in English]

the current is concentrated that is the smaller the area of contact between the conductor and the skin the greater the heat per unit area and the severer the burn The current may or may not be sufficient to cause electric shock If the area of contact is large the heat per unit area may be insufficient to burn but the current amperage may cause electric shock. The heat generated in t seconds by the passage of an electric current through a resistance is dependent on the voltage current and resistance and is governed by the following formulae

$$\text{Calories} = \frac{CV}{4\ 18}t = \frac{C^2R}{4\ 18}t = \frac{V^2}{4\ 18R}t$$

where C = current in amperes, V = potential in volts and
R = resistance in ohms

Thus the rate of generation of heat increases with the squares of the amperage and voltage other factors remaining constant This explains why currents of high amperage at low or moderate voltage passing for a fraction of a second may produce severe burns although the time limitation may be too brief for severe shock and also why burns from high tension currents are generally so much more severe than low tension burns Edwards and Bowie (1940) believe that the charring of the skin and the destruction of deeper tissues is more extensive the higher the pressure up to 5 000 or 10 000 volts, but many high tension burns must be a combination of electrothermal arc burns and electric contact burns The question is complicated by other factors such as the frequency of the alternating current and changes in the resistance of the skin during the passage of the current. Emerson (1956) remarked that perhaps the worst burns are those due to high frequency and Jolly and Gaertner (quoted by Jaffé 1928) report that the skin resistance may greatly decrease as the current passes through but that the development of burns increases the resistance

The order of resistance of animal tissues is bone > fat > skin > tendon > muscle > blood > nerve (Pack 1926) Compared to that of the skin the resistance of the rest of the body is negligible It has often been stated that the higher the resistance of the skin the greater the severity of burning and vice versa (Pack 1926 Gaby 1927 Fisher 1937) but the truth of this must be limited Skin resistance varies considerably between different persons and in different areas of the same person. It may range from hundreds of thousands of ohms in the dry thick skin of manual workers to 1 000 ohms or less in thin wet skin but it usually ranges from 3 000 to 5 000 ohms (Gaby 1927 Jaffé 1928) A low skin resistance will permit more current to pass will drop the voltage less and may produce electric shock

example, Jellinek, 1912, 1936), others distinguish the skin lesions produced by the entrance of electricity, the current markings, from burns produced by electric sparks and ignition of clothing (Jaffé, 1928) or from arcing of the current (Fisher, 1937), whilst others classify the burns into contact and flash or arc burns (Gaby, 1927, Wells, 1929) Indeed Wells (1929) believes that the contact burn results from arcing of the current in the skin

Most workers agree that the lesions should be classified according to the mechanism of injury even though in the final analysis all burns from electricity are due to heat The following division is proposed

(1) *Electric contact burns*, or true electric burns, which are caused by an electric current passing through the skin after contact with a conductor and which are associated with the passage of electricity through the body (Fig 84) This includes the "current markings" of other writers

(2) *Electrothermal burns* which result from the electrical generation of heat outside the skin and may be subdivided into (a) *flash* or *arc burns* and (b) *contact burns*

The burns which follow the leaping of an electric arc from the conductor to the skin are mainly associated with high tension currents They are severe and deep because an electric arc has a temperature between 2,500°C and 3,000°C Cases have been recorded in which deep holes have been produced in bones through their liquefaction

Electrothermal contact burns are caused through contact with a red or white hot resistance such as the radiant of an electric fire They may be produced without the passage of a current through the body, as for example when the grounding is insulated, but in other cases an electric contact burn also occurs and is masked by or combined with the electrothermal lesion Electric shock or the presence of an exit burn remote from the site of contact or arcing discloses that a current had passed through the body

(3) *Flame burns* result from the ignition of clothing by electrical sparks and arcing An extensive area of the body may be burned and this may dominate other lesions

Electric contact burns.—These are characterized by coagulation necrosis extending into or beyond the subcutaneous tissues, by slow separation of the slough and by delay in healing The current passes through a part of the body and the burns occur at the sites of skin entry and exit because they are the points of greatest resistance Both alternating currents (A C) and direct currents (D C) produce contact burns, which suggests that the generation of heat and not electrolysis is the cause of the lesion Presumably the heat is generated through a dropping of the voltage across the resistance of the skin

The capacity for burning depends on the amount of heat generated per second per unit area of skin Other factors being equal the more

the current is concentrated that is the smaller the area of contact between the conductor and the skin the greater the heat per unit area and the severer the burn The current may or may not be sufficient to cause electric shock If the area of contact is large the heat per unit area may be insufficient to burn but the current amperage may cause electric shock The heat generated in t seconds by the passage of an electric current through a resistance is dependent on the voltage current and resistance and is governed by the following formulae

$$\text{Calories} = \frac{CV}{4\ 18}t = \frac{C^2R}{4\ 18}t = \frac{V^2}{4\ 18R}t$$

where C = current in amperes V = potential in volts and R = resistance in ohms

Thus the rate of generation of heat increases with the squares of the amperage and voltage other factors remaining constant This explains why currents of high amperage at low or moderate voltage passing for a fraction of a second may produce severe burns although the time limitation may be too brief for severe shock and also why burns from high tension currents are generally so much more severe than low tension burns Edwards and Bowie (1940) believe that the charring of the skin and the destruction of deeper tissues is more extensive the higher the pressure up to 5 000 or 10 000 volts, but many high tension burns must be a combination of electrothermal arc burns and electric contact burns The question is complicated by other factors such as the frequency of the alternating current and changes in the resistance of the skin during the passage of the current Emerson (1956) remarked that perhaps the worst burns are those due to high frequency and Jolly and Gaertner (quoted by Jaffé, 1928) report that the skin resistance may greatly decrease as the current passes through but that the development of burns increases the resistance

The order of resistance of animal tissues is bone fat > skin tendon muscle blood nerve (Pack 1926) Compared to that of the skin the resistance of the rest of the body is negligible It has often been stated that the higher the resistance of the skin the greater the severity of burning and vice versa (Pack 1926 Gaby 1927 Fisher 1937) but the truth of this must be limited Skin resistance varies considerably between different persons and in different areas of the same person It may range from hundreds of thousands of ohms in the dry thick skin of manual workers to 1 000 ohms or less in thin wet skin but it usually ranges from 3 000 to 5 000 ohms (Gaby 1927 Jaffé 1928) A low skin resistance will permit more current to pass will drop the voltage less and may produce electric shock

example, Jellinek, 1912, 1936), others distinguish the skin lesions produced by the entrance of electricity, the current markings, from burns produced by electric sparks and ignition of clothing (Jaffé, 1928) or from arcing of the current (Fisher, 1937), whilst others classify the burns into contact and flash or arc burns (Gaby, 1927, Wells, 1929) Indeed Wells (1929) believes that the contact burn results from arcing of the current in the skin

Most workers agree that the lesions should be classified according to the mechanism of injury even though in the final analysis all burns from electricity are due to heat The following division is proposed

(1) *Electric contact burns*, or true electric burns, which are caused by an electric current passing through the skin after contact with a conductor and which are associated with the passage of electricity through the body (Fig 84) This includes the "current markings" of other writers

(2) *Electrothermal burns* which result from the electrical generation of heat outside the skin and may be subdivided into (a) *flash* or *arc burns* and (b) *contact burns*

The burns which follow the leaping of an electric arc from the conductor to the skin are mainly associated with high tension currents They are severe and deep because an electric arc has a temperature between 2,500°C and 3,000°C Cases have been recorded in which deep holes have been produced in bones through their liquefaction

Electrothermal contact burns are caused through contact with a red or white hot resistance such as the radiant of an electric fire They may be produced without the passage of a current through the body, as for example when the grounding is insulated, but in other cases an electric contact burn also occurs and is masked by or combined with the electrothermal lesion Electric shock or the presence of an exit burn remote from the site of contact or arcing discloses that a current had passed through the body

(3) *Flame burns* result from the ignition of clothing by electrical sparks and arcing An extensive area of the body may be burned and this may dominate other lesions

Electric contact burns.—These are characterized by coagulation necrosis extending into or beyond the subcutaneous tissues, by slow separation of the slough and by delay in healing The current passes through a part of the body and the burns occur at the sites of skin entry and exit because they are the points of greatest resistance Both alternating currents (A C) and direct currents (D C) produce contact burns, which suggests that the generation of heat and not electrolysis is the cause of the lesion Presumably the heat is generated through a dropping of the voltage across the resistance of the skin

The capacity for burning depends on the amount of heat generated per second per unit area of skin Other factors being equal the more

because the skin is often scorched and may be disrupted by radiating tears

An inflammatory reaction of the burned skin is not possible because it is heat-coagulated but by 24–48 hours a peripheral zone of erythema appears and the tissues around and deep to the burn swell with oedema

Pathology —The burn is deeper than ordinary flame burns it extends into the subcutaneous tissue, and deeper structures tendons muscles, nerves and even cartilage and bone may be destroyed deep to the point of contact. Necrosis is the dominant feature of the lesion Coagulation necrosis from heat is responsible for the appearance of the skin and the immediate death of deeper tissues, but later exten sion of necrosis is at least partly due to ischaemia from arterial lesions

Histologically the epidermis is shrunken and the nuclei particu larly in the basal-cell layer are elongated into spindles The dermal papillae are flattened and the collagen bundles are coarse, swollen and often basophilic At the edge the demarcation between normal and affected skin is fairly sharp Deep to the area of coagulation the tissues are swollen congested and loosely infiltrated with poly morphs The essential changes are like those seen in severe heat burns (Chapter 2) Medico-legally it should be borne in mind that vital processes are not responsible for the necrotic skin changes which could be produced after death

Internal destruction may be extensive and tends to progress beyond the limits visible after the accident Internal necrosis is particularly large when the entry and exit of the current were in the same limb especially when the current was high tension Tissues are then destroyed not only deep to the areas of electrical contact but also along the path of the current and the depth and extent of destruction may be out of all proportion to the mildness of the clinical symptoms The underlying muscles may be paralysed due to involvement of nerves, while parts may be necrotic sloughing later Because blood vessels are good conductors of electricity vascular and other lesions may be produced even remote from the points of contact Extreme spasm and thrombosis of arteries and necrosis of their walls may extend the area of necrosis and produce fish flesh ischaemic necrosis of muscles Indeed gangrene of part or the whole of a limb may occur either related to the entrance or emergence of the current Parts of the media of vessels may be weakened by cellular disinte gration and if thrombosis does not occur the lesion may lead to serious haemorrhage

whereas a higher skin resistance under the same conditions will produce a burn On the other hand the very high resistance of thickly calloused skin may act as an insulator and prevent the passage of a current, then neither shock nor burning will occur Perhaps within certain limits the greater the resistance of the skin the severer is the burn, but experimental investigations are required to separate fact from theoretical deduction

Appearance —The burns occur at the entrance and exit of the current The hands are often burned because of the nature of electrical work and the soles are often involved when the current enters the ground through the feet When the entrance and exit burns are in the same

FIG 84 —Multiple electric contact burns of fingers

limb considerable internal destruction is likely Damage at the current entry is generally more severe than at the exit

The burns vary from one or more roughly circular spots a few millimetres in diameter to areas of destruction centimetres across, but the depth and extent of burning are often grossly underestimated when first seen Sometimes early examination reveals little and several days later areas of necrosis become obvious Usually the lesion appears as an ischaemic whitish or yellowish coagulated area, slightly depressed, dry and painless, part of it may be charred The lesion is circumscribed and the edges are generally well defined In small burns (Fig 84) the edges are often slightly raised and the centre may be excavated and ragged Fragments of metal derived from the conductor may be found at the point of contact and may be important medico-legally, and a groove the shape and size of the live wire may be present Pack (1926) compared the exit lesion to a gunshot wound

because the skin is often scorched and may be disrupted by radiating tears

An inflammatory reaction of the burned skin is not possible because it is heat-coagulated, but by 24–48 hours a peripheral zone of erythema appears and the tissues around and deep to the burn swell with oedema

Pathology —The burn is deeper than ordinary flame burns it extends into the subcutaneous tissue and deeper structures tendons muscles, nerves and even cartilage and bone may be destroyed deep to the point of contact Necrosis is the dominant feature of the lesion Coagulation necrosis from heat is responsible for the appearance of the skin and the immediate death of deeper tissues but later extension of necrosis is at least partly due to ischaemia from arterial lesions.

Histologically the epidermis is shrunken and the nuclei particularly in the basal-cell layer are elongated into spindles The dermal papillae are flattened and the collagen bundles are coarse, swollen and often basophilic At the edge the demarcation between normal and affected skin is fairly sharp Deep to the area of coagulation the tissues are swollen, congested and loosely infiltrated with polymorphs The essential changes are like those seen in severe heat burns (Chapter 2) *Medico-legally it should be borne in mind that vital* processes are not responsible for the necrotic skin changes which could be produced after death

Internal destruction may be extensive and tends to progress beyond the limits visible after the accident Internal necrosis is particularly large when the entry and exit of the current were in the same limb especially when the current was high tension Tissues are then destroyed not only deep to the areas of electrical contact but also along the path of the current and the depth and extent of destruction may be out of all proportion to the mildness of the clinical symptoms The underlying muscles may be paralysed due to involvement of nerves, while parts may be necrotic, sloughing later Because blood vessels are good conductors of electricity vascular and other lesions may be produced even remote from the points of contact. Extreme spasm and thrombosis of arteries and necrosis of their walls may extend the area of necrosis and produce fish flesh ischaemic necrosis of muscles Indeed gangrene of part or the whole of a limb may occur either related to the entrance or emergence of the current Parts of the media of vessels may be weakened by cellular disintegration and if thrombosis does not occur the lesions may lead to serious haemorrhage

The histological appearance of the dead muscle varies Immediate heat-coagulative changes are disclosed by the altered appearance of the nuclei even though the cross-striations and general structure of the sarcoplasm may be preserved, and by changes in the intramuscular collagen The intramuscular arteries may be tightly closed as if in spasm and their walls may be necrotic Severe degenerative or necrobiotic changes produce irregular swelling of the muscle fibres, various kinds of sarcoplasmic degeneration, including granular changes and altered staining properties, and nuclear abnormalities including focal areas of irregularity and fragmentation Some areas may be infiltrated by polymorphs, some of which congregate at patches of disrupted sarcolemma The capillaries may be engorged and an eosinophilic oedema may be visible

Course —Left alone the area of aseptic necrosis finally comes away as a slough either in one piece or in a number of pieces at different times, but this may take weeks After demarcation luxurious granulation tissue develops Jellinek and others state that the wounds then possess an extraordinary tendency to heal, that the course of healing is smooth and that the residual scar is thin He adds that haemorrhage is not uncommon and may be serious Infection however may occur and ugly scar contractures may be produced (Wells, 1929, Critchley, 1935)

Treatment —Many surgeons have insisted that electric burns should be treated conservatively because (1) there is an initial difficulty in determining the depth and internal extent of necrotic tissue which has to be excised, (2) the danger of secondary haemorrhage after operation is possibly increased and (3) healing is excellent once the wound has sloughed Jellinek (1936), who had an experience of over 4,000 cases, stated that serious complications occur only when active surgery is performed, and that with conservative treatment the lesions never went septic or gangrenous and healed well He warns against unnecessary amputations and points out that even when large joints have been laid bare healing occurs without complications and without ankylosis Wells (1929) was critical of conservative therapy largely because natural healing took such a long time He advocated primary excision, suture and grafting which he claimed was successful in the great majority of cases He admitted that early surgical excision sometimes had limitations because the junction of living and dead tissue might not be sufficiently clear to warrant immediate excision In Birmingham, a surgical exploration of the burned area and, if necessary the surrounding tissues is performed a few days after burning to determine the extent, depth and location

of tissue necrosis and this is immediately followed by excision and grafting (Jackson 1956)

ELECTRIC SHOCK

The passage of an electric current through the body may merely cause a slight tingling but severe shock or almost instantaneous death may be produced The severity of symptoms depends on many factors, the most important of which are (1) individual susceptibility (2) voltage (3) amperage (4) nature of current (A C or D C) (5) the frequency of cycles (if A C) (6) duration of contact, (7) resistance of the skin (8) path of the current through the body (9) resistance of the body and (10) the adequacy of grounding

Jellinek (1936) stressed that constitutional and psychical factors in man are far more important than the amperage or voltage which have been stressed in experimental work Nevertheless shock is likely to be more serious at higher voltages but death may follow contact with ordinary domestic current and fatal shock has been known to happen at a potential of 45 volts or less A.C is more dangerous than D C and the usual domestic frequency of 50 cycles per second is particularly hazardous The effects of current of different amperages passing through the body from hand to hand or hand to foot have been summarized by Emerson (1956) Currents up to 6 milliamperes (mA) cause a slight tingling effect which to some people is a pleasant sensation Currents from 10 to 15 mA produce muscular contraction so that it is difficult to release the charged conductor this may cause death even at low voltages if the muscular spasms extend to the chest muscles and impede respiration but immediate artificial respiration is invariably effective Prolonged exposure to between 10 and 30 mA will kill most people A current of 100 mA will kill if it persists and can kill in a fraction of a second particularly if it passes through the heart. Currents above 100 mA are generally fatal Emerson adds that 10 mA for a second is the maximum safe current through the heart.

The points of electrical contact determine the path of the current and this tends to pursue the shortest course between entry and exit (Weeks and Alexander 1939) When the flow passes through the heart in experimental animals it causes heart fibrillation and death when the current approaches 100 mA and the same current through the brain stem is said to produce respiratory and vasomotor paralysis

The resistance of contact and of the body are important Current passing through a conductor obeys Ohm s Law (voltage = amperage resistance in ohms) Good contact and good grounding facilitate the flow of current and increase the risk of shock Skin resistance

is much reduced by sweating or immersion in water, which also increase the shock Research however has shown that Ohm's Law is not really applicable to the body Within limits the lower the voltage the higher the apparent resistance of the body (quoted by Emerson, 1956) The body resistance is minimal when the current tension is above about 120 volts but decreasing the voltage to 50 may quadruple the resistance Therefore lowering the voltage will disproportionately lower the current passing through the body and this partly explains why high voltages are more dangerous than low ones This adds further weight to the recommendations of the Factory Inspectorate in Britain to reduce the voltage of all electrical tools and instruments in the interests of safety

Pathological effects—A severe electric shock may cause immediate unconsciousness, but this is not invariable The victim can remain unconscious for minutes, hours or a day and exhibit convulsions, twitchings and tremors At first the brain may be stimulated and then nerve centres may be paralysed Blood vessels are sent into spasm Jellinek (1936) says that sometimes the cerebrospinal fluid pressure is rapidly increased and produces cerebral compression Ischaemic necrosis of muscles with myohaemoglobinuria and even gangrene of limbs may occur from vascular spasm and thrombosis in those who survive long enough In such patients anuria and uraemia from renal failure is a special hazard Longitudinal fissure fractures of long bones are sometimes caused by the passage of the current Indeed every organ in the body can be affected through electric injury, either directly by the current or indirectly through electric shock or other means

Necropsy of electrocuted subjects does not reveal pathognomonic findings except for electric contact burns which are usually present at the sites of entry and often the exit of the current The lungs are usually congested and oedematous and the heart dilated and flaccid Petechiae are found on the pleura and epicardium, and small haemorrhages, often perivascular, are common in the brain and meninges but these are probably secondary to circulatory anoxia Shrinkage and chromatolysis of ganglion cells may be found Other neuropathological effects of accidental electrocution include areas of perivascular demyelination and disintegration, and swelling of macroglial and oligodendroglial cells (Alexander, 1938)

Mechanism of death—There are two views about the cause of death (1) Death is due to respiratory failure from paralysis of the respiratory centre, usually associated with vasomotor failure, and (2) death results from acute cardiac failure from ventricular fibrillation

or cardiac inhibition Support for the cardiac mode of death is largely based on observations in animals whilst those who oppose this view and adhere to respiratory paralysis are influenced by observations in accidently electrocuted men (*see* Jaffé 1928) The mode of dying is important because ventricular fibrillation almost inevitably causes death regardless of first aid therapy whilst respiratory failure may be treated by artificial respiration Jellinek (1912 1936) and others insist that death is usually due to respiratory failure, that the respiratory centre is at first refractory to stimuli but if oxygenation is continued by artificial means the brain stem may recover and the victim be saved Both views are probably correct in different cases and it may be that respiratory failure is more common The feeble circulation and low blood pressure in such cases may result from vasomotor paralysis It is uncertain whether the current has to pass through the brain to produce respiratory failure but the use of large currents in electroconvulsive therapy suggests that this is not the mechanism and Spilsbury (quoted by Jaffé, 1928) thought that respiratory paralysis was reflexly produced through sensory stimuli A number of workers believe that high voltages cause death from central respiratory failure and low voltages through ventricular fibrillation

Sequelae—The remote effects said to be produced by electric shock are numerous and include optic atrophy cataract and various organic and functional diseases of the brain and spinal cord, none of which are common (Critchley 1935) Cases of disseminated sclerosis, parkinsonism, cerebral tumour myasthenia gravis amyotrophic lateral sclerosis, post-concussional syndrome and psychological disorders have been reported but the causal role of electric shock has not always been established Although the *post hoc ergo propter hoc* fallacy must be borne in mind medico-legally the patient should be given the benefit of any doubt.

Resuscitation.—Because respiratory paralysis may be reversible and at first death is only apparent, the victim's life may be saved by commencing artificial respiration *immediately* and if necessary continuing it for hours The conventional Sylvester and Schafer methods of applying artificial respiration have been largely superseded by the Holger Nielsen method in which arm lift and scapular pressure are applied (Ministry of Labour and National Service 1954)

If possible, artificial respiration should be combined with inhalation of oxygen but an oxygen-carbon dioxide mixture is not recommended The deliberate administration of carbon dioxide is

unwarranted because the normal protective mechanism against the rise of body carbon dioxide to poisonous levels has been lost

CHEMICAL BURNS

Burns from chemicals may be divided into those caused by (1) strong acids alkalis and miscellaneous chemicals and (2) mustard gas, lewisite and other vesicants used in war

BURNS FROM ALKALIS, ACIDS AND OTHER AGENTS

Most of these are caused accidentally by the splashing of the liquid chemicals in industrial plants and laboratories and they commonly involve the hands and face or other exposed parts The changes produced by strong acids and alkalis resemble those produced by heat in many ways but the burns may progress in depth quite unlike heat burns the depth of which is restricted by the poor conductivity of the skin and by the short time of action of the heat (Chapter 1) A typical acid or alkali burn shows three areas A peripheral area of hyperaemia and oedema surrounds the necrotic area the centre of which may show lysis Histologically the changes are similar to the effects of heat (Fig 85)

The activity of alkalis is due to their dissociated OH ions and it is possible that when these combine with the tissues more OH ions are liberated and continue the action on deeper tissues The H ions of strong acids may act in the same way Any considerable excess of either H or OH ions is incompatible with cell life

Alkali burns—Caustic alkalis like *sodium* and *potassium hydroxide* act by combining with the tissues to form alkali proteinates, by saponifying fats and through their hygroscopic action of abstracting interstitial and intracellular water (Pack, 1926) Unlike strong acids visible evidence of injury is delayed (Davidson, 1927) Gradually the skin becomes macerated and a thick oedematous slough develops The depth of sloughing varies with the concentration of the agents and their time of action The slough which forms is soluble and consequently part of the affected skin may liquefy

Lime (calcium oxide) has no effect on dry skin but burning can be produced if the lime is wetted after skin contact because the formation of calcium hydroxide liberates a considerable quantity of thermal energy and may boil the water (Davidson, 1927), although calcium hydroxide has little or no caustic action When action on the skin has begun the necrosis may extend because of the avidity of lime for tissue water Burns from cement are due to the large amount of calcium oxide present

Acid burns.—Strong mineral acids are also hygroscopic and dehydrate the skin (Fig. 85). They also precipitate proteins, form acid albumins and soften or dissolve epithelium or connective tissue. The liberation of heat from solution in tissue water increases the depth of burning and may produce or increase charring. Perhaps the deepest burns are produced by hydrofluoric acid. Unlike concentrated alkalis concentrated mineral and organic acids produce a prompt visible reaction but with dilution of the acid there is a delay before changes are visible (Davidson 1927). Concentrated *sulphuric*

FIG. 85.—Sulphuric acid burn of the forehead excised 6 hours after the accident. The keratin layer is absent and the remainder of the epidermis is shrunken, dehydrated and coagulated. The dermal collagen is largely coagulated, the hair follicles show nuclear pyknosis and distortion and many have been torn by rents and fissures. (Haematoxylin and eosin × 100.)

acid has a tremendous avidity for water and its action on skin is vigorous. Not only does it withdraw tissue water but it carbonizes the tissues and produces a brown or blackish slough. The affected area is surrounded by red, oedematous skin. Strong *nitric acid* is a strong caustic, produces a deep coagulation and leaves a yellow slough because of its xanthoprotein reaction with tissue proteins. Concentrated *hydrochloric acid* is less efficient as a caustic than sulphuric or nitric acids and usually leaves a yellowish brown stain.

Organic acids which can affect the skin include acetic acid, carbolic acid (phenol), trichloroacetic acid and oxalic acid. *Acetic acid* is not a vigorous caustic but the concentrated acid produces an intensely inflamed necrotic skin (Davidson 1927). *Carbolic acid* coagulates

proteins and destroys enzymes, and *lysol* has a similar action The affected area may turn a greenish-black colour These substances are readily absorbed through the skin, systemic poisoning may result and the phenolic substances are excreted in the urine Anuria and uraemia from renal tubular necrosis is a particular hazard *Trichloroacetic acid* is a potent protein precipitant and rapidly produces a white necrotic skin There is some experimental evidence that the substance can also be absorbed through the skin and thus produce toxic effects *Oxalic acid* is not a strong caustic but is a very dangerous poison when absorbed

Other chemicals.—*White phosphorus* produces deep burns for two reasons Firstly the element burns when exposed to the air, rapid oxidation occurs and much heat is generated during the process Secondly the phosphorus pentoxide formed has a strong hygroscopic and corrosive action on the skin *Bromine* and the acid salts of *zinc* and *tin* chloride may also produce burns on occasion

Clinical implications

First-aid—Skin splashed with acid or alkali should be immediately placed under a stream of running water to wash away the chemical Burns from lime should not be treated with water until as much as possible of the powder has been brushed off Burning phosphorus adherent to the skin can be extinguished by immersion under water Copper sulphate solution may also be applied

In the past the treatment of acid burns with dilute alkali such as bicarbonate of soda, and alkali burns with weak acetic or citric acid was recommended, but without an indicator it is not possible to know when the chemical is neutralized, and over-enthusiastic therapy may do harm In an experimental investigation on rats Davidson (1927) found that burns produced by strong acids or alkalis had a much better clinical course after immediate washing with a large quantity of water than after immediate neutralization with bicarbonate or acetic acid respectively In recent years buffered phosphate solutions have been introduced for acid and alkali burns Some industrial firms, the employees of which run a risk from acids or alkalis, keep tanks of buffered phosphate solution for first-aid use Immediately after an accident the tap is turned and the affected part is bathed in a stream of solution This procedure retains the advantage of continuous diluting and washing away of the chemical on and in the skin and also has a neutralizing action All industrial plants in which strong acids and alkalis are used should install these tanks In the Birmingham Accident Hospital a strong phosphate buffer solution at *p*H7 is used to irrigate both acid and alkali burns

and may be applied as a compress thereafter Such a solution has the added advantage that it can be used to wash out the mouth or irrigate the eye if these are affected

Depth of burning —Acid burns including those from carbolic acid usually produce an *insensitive* coagulated skin Many subsequently prove to be full thickness burns but others prove to be partial skin loss burns (Jackson 1953) This means that analgesia to pinprick (*see* Chapter 4) cannot be used as a differential sign between partial and full thickness-loss burns from these agents and that the burns should not be treated by primary excision and grafting but should be given a chance to heal naturally

WAR VESICANTS

These are chemicals which combine two properties (1) that of being severe skin irritants even at low dilutions producing inflammation and blistering of the skin and (2) that of a systemic poison The best known ones are the sulphur and nitrogen mustards and the arsenical vesicant lewisite The systemic effects are produced after absorption through the skin These agents differ from strong acids and alkalis in that they are profoundly toxic to cells in low concentrations at which they are not general protoplasmic precipitants

Mustard gas.—First discovered in 1859 by Guthrie who commented on its vesicant properties, mustard gas is chemically 2, 2 dichlorodiethyl sulphide It is potent in the vapour state as well as in the liquid phase (*see* Cullumbine 1947) It penetrates the skin rapidly but there is a latent period of some hour before skin changes are visible Eighty to ninety per cent passes into the circulation and the remainder is rapidly fixed in the skin possibly combining with proteins No "free vesicant can be found 5 minutes after contamination Application of anti gas ointments which are highly penetrating chlorinating compounds, is only effective within a few minutes There are three biochemical views with regard to its vesicant action (1) Dixon s hypothesis that it inactivates the skin hexokinase enzyme system but unlike lewisite, sulphydryl groups are not its primary site of attack (2) that it attacks the — COOH groups in proteins and (3) that its primary attack is on the surface of cells (*see* Peters, 1947) Although obvious vesication and erythema are delayed the skin capillaries become excessively permeable within a few minutes of contamination and within 30 minutes there is histological evidence of damage to the dermis Leukotaxine can be readily isolated from the contamined skin and from the blister fluid and this suggests that it may be responsible at some stage for the inflammatory change

proteins and destroys enzymes, and *lysol* has a similar action The affected area may turn a greenish-black colour These substances are readily absorbed through the skin, systemic poisoning may result and the phenolic substances are excreted in the urine Anuria and uraemia from renal tubular necrosis is a particular hazard *Trichloroacetic acid* is a potent protein precipitant and rapidly produces a white necrotic skin There is some experimental evidence that the substance can also be absorbed through the skin and thus produce toxic effects *Oxalic acid* is not a strong caustic but is a very dangerous poison when absorbed

Other chemicals.—*White phosphorus* produces deep burns for two reasons Firstly the element burns when exposed to the air, rapid oxidation occurs and much heat is generated during the process Secondly the phosphorus pentoxide formed has a strong hygroscopic and corrosive action on the skin *Bromine* and the acid salts of *zinc* and *tin* chloride may also produce burns on occasion

Clinical implications.

First-aid—Skin splashed with acid or alkali should be immediately placed under a stream of running water to wash away the chemical Burns from lime should not be treated with water until as much as possible of the powder has been brushed off Burning phosphorus adherent to the skin can be extinguished by immersion under water Copper sulphate solution may also be applied

In the past the treatment of acid burns with dilute alkali such as bicarbonate of soda, and alkali burns with weak acetic or citric acid was recommended, but without an indicator it is not possible to know when the chemical is neutralized, and over-enthusiastic therapy may do harm In an experimental investigation on rats Davidson (1927) found that burns produced by strong acids or alkalis had a much better clinical course after immediate washing with a large quantity of water than after immediate neutralization with bicarbonate or acetic acid respectively In recent years buffered phosphate solutions have been introduced for acid and alkali burns Some industrial firms, the employees of which run a risk from acids or alkalis, keep tanks of buffered phosphate solution for first-aid use Immediately after an accident the tap is turned and the affected part is bathed in a stream of solution This procedure retains the advantage of continuous diluting and washing away of the chemical on and in the skin and also has a neutralizing action All industrial plants in which strong acids and alkalis are used should install these tanks In the Birmingham Accident Hospital a strong phosphate buffer solution at pH7 is used to irrigate both acid and alkali burns

REFERENCES

Alexander L. (1938) *J Industr Hyg.*, 20 191
Critchley M (1935) *Lancet* 2, 1002
Cullumbine H (1947) *Nature* 159 151
Davidson E. C. (1927) *Ann Surg.*, 85 481
Edwards, C. R. and Bowle H C. (1940) *Amer J Surg* 47 299
Emerson S. J (1956). *Report to the Birmingham and District Industrial Safety Group*
Fisher H E. (1937) *Illinois med J* 72, 158
Gaby R. E. (1927) *Canad. med Ass J.*, 17 1343
Jackson, D McG (1953) *Brit J Surg* 40 588
— (1956) Personal communication.
Jaffé R. H (1928) *Arch. Path* 5, 836.
Jellinek, S (1912) *Atlas der Elektropathologie* Vienna Springer
— (1936) *Edinb med J* 43, 587
Jex Blake A. J (1913) *Brit med J* 1 425
Ministry of Labour and National Service London Factory Dept. (1954) *Form* 1705
Pack G T (1926) *Arch Path. Lab Med.*, 1 767
Peters, R. A. (1947). *Nature* 159 149
— (1947–48) *Brit med Bull* 5, 313
Report of the Chief Inspector of Factories (1954) London H.M Stationery Office.
Stocken, L. A., and Thompson, R H S (1946) *Biochem. J* 40 535 548
Weeks, A. W., and Alexander L. (1939) *J Industr Hyg.*, 21 517
Wells, D B (1929) *Ann. Surg.*, 90 1069

Formation of leukotaxine however is not specific to mustard blister fluid since it is found in oedema fluid produced by thermal burns (Chapter 3) and in the blister fluid produced by other vesicants

Mustard burns behave similarly to thermal burns and they heal in a similar fashion Epidermal regeneration in partial skin-loss burns begins about the third day and is often hypertrophic with ingrowths and "nests" of epidermal cells in the dermis (Cullumbine, 1947) Extensive contamination with the vesicant may lead to oligaemic shock, in such patients intravenous therapy is just as important as in those with ordinary burns The systemic effects are mainly on the bone marrow, lymphoid system and alimentary tract and closely resemble those produced by x-radiation Degeneration of the haemopoietic system and lymph nodes is produced

Lewisite and dimercaprol—Lewisite ($CH\,Cl \quad CH\,As\,Cl_2$) and a number of other vesicants such as dichlorodiethylsulphone and divinylsulphone are of special interest because skin damage and vesication are initiated by a specific biochemical lesion (*see* Peters, 1947–48) The systemic effects of lewisite are like those of inorganic arsenic—vomiting, diarrhoea and circulatory collapse, and possibly an acute haemolytic reaction

Peters, Voegtlin and their colleagues showed that *arsenical* vesicants produce their toxic effects by interfering with the —SH (thiol) components of the pyruvate-oxidase enzyme system This concept, which was an extension of Ehrlich's chemoreceptor theory, led to a search for substances with thiol groupings which would compete for and combine with the active chemical groupings of the vesicant and thereby prevent it from injuring the skin It was found that compounds with two —SH groups were necessary to interfere with vesicant action and Stocken and Thompson (1946) prepared 2 3 dimercaptopropanol (dimercaprol, British-anti-lewisite, B A L) which was effective in preventing lewisite burns When dimercaprol is applied to contaminated skin its thiol groups not only combine with the arsenical more readily than those on the skin thereby preventing vesication, but it can even reverse the tissue thiol-arsenical reaction provided that contamination with lewisite had occurred only 1 or 2 hours previously Further work showed that dimercaprol is an effective antidote to poisoning by arsenic, mercury, gold, antimony and other metals

The discovery of dimercaprol and the theoretical considerations leading to it have repercussions on pathology As Peters (1947–48) points out it was the first instance in which commencing damage to tissues could be reversed by chemical interference

REFERENCES

Alexander L. (1938) *J Industr Hyg.*, 20 191

Critchley M (1935) *Lancet* 2, 1002.

Cullumbine, H (1947) *Nature* 159 151

Davidson, E. C (1927) *Ann Surg* 85 481

Edwards, C. R., and Bowne, H C (1940) *Amer J Surg.*, 47 299

Emerson, S J (1956) *Report to the Birmingham and District Industrial Safety Group*

Fisher H E. (1937) *Illinois med J.*, 72, 158

Gaby R E. (1927) *Canad med Ass J* 17 1343

Jackson, D McG (1953). *Brit J Surg* 40 588

— (1956) Personal communication.

Jaffé R H (1928). *Arch Path.*, 5, 836

Jellinek S (1912) *Atlas der Elektropathologie* Vienna Springer

— (1936) *Edinb med J.*, 43 587

Jex Blake, A. J (1913) *Brit med J* 1 425

Ministry of Labour and National Service, London Factory Dept. (1954) *Form* 1705

Pack, G T (1926) *Arch Path. Lab Med* 1 767

Peters, R. A. (1947). *Nature* 159 149

— (1947–48) *Brit med. Bull.*, 5, 313

Report of the Chief Inspector of Factories (1954) London H M Stationery Office.

Stocken, L. A., and Thompson, R. H S (1946) *Biochem J* 40, 535 548

Weeks, A. W., and Alexander L. (1939) *J Industr Hyg* 21 517

Wells, D B (1929) *Ann Surg* 90 1069

INDEX OF AUTHORS

N*

SUBJECT INDEX

A

B

U

V

W

X